HARVARD UNIVERSITY MONOGRAPHS IN MEDICINE AND PUBLIC HEALTH

Number 10

PHYSIOLOGY IN DISEASES OF THE HEART AND LUNGS

BY

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HARVARD UNIVERSITY PRESS
CAMBRIDGE · MASSACHUSETTS
1950

PRINTED IN THE UNITED STATES OF AMERICA

Second Printing

LONDON · GEOFFREY CUMBERLEGE
OXFORD UNIVERSITY PRESS

TO MY PARENTS

Members of that vanishing species, the Old-World Idealistic Intellectual

PREFACE

This monograph was written because a number of third- and fourth-year students at the Harvard Medical School requested it. That these men felt a need, or at least a desire, for a work of this sort should be of interest to those who are engaged in the teaching of the various branches of medicine.

The third and fourth years of medical school are often regarded as a period of adolescence, when the painful transition from student in the laboratory and classroom to the well-rounded, though still inexperienced, clinician occurs. According to this concept, a book such as this helps to overcome to some extent the insecurity and bewilderment of this difficult period While this point of view possibly applies to a small number of the students, it does not appear to be valid for most. It does not, moreover, accurately describe the place of laboratory science in medical education, for, in the words of Bacon, it causes the former to be "degraded most unworthily to the situation of a handmaid, and made to wait upon medicine, . . . and to wash the immature minds of youth and imbue them with a first dye, that they may afterwards be more ready to receive and retain another"

The last two years of the course in medical school resemble for most students a honeymoon period; the men have finally attained their desire, clinical medicine, and never again will it seem so wonderful to them or will they learn so much about it so quickly — and at times, so painfully. The attitude of these students consists in large part of fascinated and amazed delight with the variety, complexity and subtlety of the manifestations of disease, together with a desire for more knowledge concerning them which is not easily appeased. The fact that many of these men wish to refer back to the details of the fundamental sciences of the preclinical years is not a manifestation of insecurity regarding clinical medicine or of lack of satisfaction with it. Rather it is an expression of the desire to enhance their appreciation and understanding of clinical phenomena.

Celsus observed that medicine was the earliest of the sciences to use experiment and most physicans since then have realized that, while it may be possible to practice clinical medicine satisfactorily without a knowledge of fundamental science, it is not possible to do any thinking about medicine without such knowledge. Attempts are made at some medical schools to satisfy the need of the thinking student for continuous contact with laboratory science in one of two ways· by giving a course of lectures or seminars during the third or fourth year designed to correlate the clinical with the preclinical, or by having the student in the fourth year retire for a period from the clinic and return to the laboratory. Both of these devices, while advantageous in some respects, are in many ways defective. A course of lectures or seminars must be given at stated intervals and consequently, coming into conflict with other assigned work, must be limited in regard to time. The content, spirit and tempo of the course are largely determined by the members of the faculty who preside and active participation by all the students is impossible. The course is arranged to cover many fields and covers none of them well, and since it is designed to fit the needs of many students, suits none completely. On the other hand, requiring that the student spend part of his fourth year in the laboratory is also not desirable. The work done there is often little more than a review of material covered in the first two years, or if investigative work is required, the student is forced to concentrate on one minute field.

An additional approach to the problem is afforded by a work such as the present one Material is here made available and is at hand at all times, but it is left to the student to obtain as much or as little as he feels he needs, at such times as he chooses. The student may be stimulated to look into this book for the explanation of an unusual or, to him, unexpected clinical phenomenon, or he may merely browse through it when he feels no urge to do anything else.

Many practicing clinicians retain some of the viewpoints and attitude of the student; indeed, it appears to be characteristic of outstanding physicians to do so. Men of this type may also find a work of this sort useful. "Taglich entschwindet die Möglichkeit nicht bloss einer Prufung, sondern selbst eines Verständnisses der neueren Schriften denjenigen mehr und mehr, welche in den oft so mühseligen und erschöpfenden Wegen der Praxis ihre beste Kraft

verbrauchen müssen," * Virchow said. The fact that there is little of practical everyday usefulness here is inherent in the nature of this work. Certainly there are available enough excellent clinical texts to supply any need in that direction.

Theoretical considerations have not been emphasized here, for "when facts are numerous, and unquestionable and unequivocal in their significance, theory must follow them as best it may, keeping time only with their step, and not go before them, marching to the sound of its own drum and trumpet." Those who are interested in a physiological discussion of disease will want the data and will be less concerned with the concepts that any author may derive from them. As in other branches of learning, Gresham's law of scholarship applies here, the commentaries have in large measure submerged the original data. Accordingly, an analysis of the conclusions derived by the large number of workers would interest only the historian. Besides, conclusions may sound as authoritative and be as misleading as the striking of hours by a wrong clock For the most part, in the work reviewed here, there are no important discrepancies between data and conclusions except in the case of an occasional mistaken investigator who, like the squid, beclouds the issue with jets of ink as he proceeds erratically backwards. Accordingly, the present work has been designed primarily as a review of data included in scientific papers and not of the conclusions derived from them. Some of the research workers whose data are included here may be surprised or even annoyed by the fact that some of these data have been used to support concepts different from or opposite to those derived by the original authors However, the use of published data in this manner requires no justification. Moreover, the interpretations here employed will undoubtedly undergo revision in the future.

It has been considered important to review all available data in the fields here covered, including the older work. Not infrequently "time, like a river, bears down to us that which is light and inflated, and sinks that which is heavy and solid" Many of the earliest studies, now neglected, contain important contributions not found in more

* Frank Chance, translator of Virchow's *Cellularpathologie*, has translated this sentence as follows "Day by day do those who are obliged to consume their best energies in the frequently so toilsome and so exhausting routine of practice find it becoming less and less possible for them, not only to closely examine, but even to understand the more recent medical works."

recent investigations. Indeed, the increasing simplification of methods has tended at times to encourage hurried and uncritical work. On the other hand, the inclusion of all available papers has resulted in a massive bibliography which "rather inclines us to admire our wealth than to perceive our poverty" Information is incomplete or lacking entirely in many fields discussed in the present work. The filling of these gaps in our knowledge of disease must wait upon the development of new techniques and concepts in the fundamental sciences; "it would be madness and inconsistency to suppose that things which have never yet been performed can be performed without employing some hitherto untried means"

It should also be noted that a large part of the physiologic and chemical research in medicine is of greater value and interest to beginning students in clinical medicine and their teachers than to any other groups. This phenomenon is interesting in itself, for it has no exact counterpart in the other professions. It may suggest an explanation for the fact that many of the best teachers in medicine also do research; indeed, in many instances their work in the laboratory is an expression of their fundamental bent toward teaching. From the administrative point of view, this situation may create difficulties in estimating proportionate time occupied in teaching and in research, and in allocating funds for each, but from the point of view of pedagogy it is a healthy thing and certainly the validity of this type of research is beyond question. "Our hope of further progress in the sciences will then only be well founded, when numerous experiments shall be received and collected into natural history, which though of no use in themselves, assist materially in the discovery of causes and axioms; which experiments we have termed enlightening, to distinguish them from those which are profitable. They possess this wonderful property and nature, that they never deceive or fail you, for being used only to discover the natural cause of some object, whatever may be the result, they equally satisfy your aim by deciding the question."

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ACKNOWLEDGMENTS

The ideas included in this work have been subjected to discussion, review and criticism by colleagues and students at the Harvard Medical School and Beth Israel Hospital. These individuals are numerous and cannot be singled out; their individual contributions are difficult to delineate and moreover naming a few to the exclusion of the rest would be unfair and not desired by the persons concerned Nevertheless, each will recognize his own part in the formation of the ideas expressed in the text

The preparation of this book for publication has been furthered by the aid afforded by a number of other persons who, by good fortune, were drawn into the enterprise. Mrs. Lucy Sagalyn transposed the original notes and typewrote the earliest drafts of the text and bibliography, this enormous task was done expeditiously in spite of other demanding duties and of difficulties consequent to the hurried and otherwise inadequate handwriting of the material presented to her. Miss Edith Morrison typewrote an intermediate draft with fidelity Mrs Francis D Judge prepared the final one with meticulous accuracy after Mr James F Ballard and his staff of the Boston Medical Library had corrected many inaccuracies in the bibliography. The Misses Mary Jane McManus and Barbara S Seamon aided Mrs Judge in verifying the accuracy of her final copy and then read the galley proof Miss Evelyn Russ helped with the galley and page proofs and Miss Marilyn M. Rapaquette typewrote the index. Mrs. Katherine R. Drinker proposed a brilliant solution to the problem raised by the large number of bibliographic references in the text; her suggestions in this regard were unique and are responsible for the manner in which this material has been arranged Mr. Joseph D Elder, of the Harvard University Press, spent long hours editing the manuscript with extraordinary care and thoroughness, the extent of his efforts is known only to him and to me The results, which are greatly appreciated by me, are evident.

CONTENTS

I

CHRONIC CARDIAC DECOMPENSATION

1. *Cardiac Output*

Discussion of the pathological physiology of chronic cardiac decompensation properly begins with consideration of the output of the heart in patients with this disorder. The great bulk of the reported data concerns the findings in cardiac patients under basal conditions, or at least at rest. Such data, while of value, give no information as to the cardiac output at a time when patients experience most or all of their symptoms, namely, during exertion; to judge from the scanty data available, values obtained during or after exertion are more strikingly abnormal than those obtained at rest.

Another source of confusion arises from the multiplicity of methods used. The reader is referred to Grollman's book (1932) for a full description of most of the methods which here will be treated only briefly. The methods used fall into two main groups: (i) those which employ the Fick principle and (ii) those which do not.

The Fick principle states that the cardiac output in cubic centimeters per minute is equal to the oxygen consumption of the body in cubic centimeters per minute divided by the arteriovenous oxygen difference per cubic centimeter of blood. In diseases in which oxygen consumption is not markedly altered, data on arteriovenous oxygen difference accordingly have the same significance as measurements of cardiac output itself. Estimation of oxygen consumption can be accomplished by means of direct, simple, and accurate methods. Determination of the arteriovenous oxygen difference, however, is beset with difficulty. While arterial blood can be secured with ease, and

so can alveolar air which is in equilibrium with it, mixed venous blood is obtainable only from the right auricle or ventricle by direct puncture or catheterization via an antecubital vein. A variety of methods for the indirect estimation of arteriovenous oxygen difference was developed in the past For technical reasons certain authors have preferred the use of carbon dioxide or various foreign gases instead of oxygen in measuring cardiac output in man. For oxygen consumption and arteriovenous oxygen difference in Fick's formula may be substituted corresponding figures for any foreign gas, or for carbon dioxide production and arteriovenous difference The technique of the method depends on the gas employed

Methods based on the Fick principle.—(*a*) *Cardiac puncture or catheterization* Oxygen consumption is measured by the usual procedures and arterial blood obtained from a convenient artery. Mixed venous blood is secured directly from the right auricle or, preferably, the right ventricle Data obtained by means of these methods in patients with congestive failure are not extensive. Values obtained by these methods in normal man are considerably higher than those obtained by the indirect methods described below (Cournand *et al.*, 1945; Stead *et al.*, 1945).

(*b*) *Analyses of arterial and peripheral venous blood.* Here again oxygen consumption is estimated by the usual methods. Blood samples taken usually from a femoral or radial artery and the antecubital or femoral vein are analyzed for oxygen or carbon dioxide in order to determine the arteriovenous difference While the use of blood from an artery is valid, since arterial blood throughout the body is of uniform composition, use of venous blood from a single portion of the body, such as the arm or leg, leads to error, since it differs from mixed venous blood. It should be noted that blood flow through skeletal muscle is small at rest (Holling, 1939), the greater part of the output of the heart being distributed to the viscera Results obtained from analysis of peripheral venous blood may indicate trends in the cardiac output, but general concepts based on such data must be accepted with reservations Strictly speaking, studies made by this method measure the blood flow only through some segment of the peripheral circulation, usually that of an extremity. Accordingly, these data will not be analyzed here but rather in Section 3 of this chapter, where peripheral blood flow is discussed.

(*c*) *Rebreathing methods.* These may be divided into two groups: (*i*) methods in which rebreathing is used to secure air in equilibrium with mixed venous blood for measurement of oxygen or carbon dioxide content and (ii) methods using a foreign gas. The latter include the nitrous oxide method (Krogh and Lindhard, 1912) and the acetylene method (Grollman, 1932). The last, in a modified form (Grollman *et al.*, 1933), is the method of this type most widely used. These methods employ measurements of rate of absorption of a foreign gas by the blood in the lungs during a period of rebreathing, and are based on the principle that the volume of gas so absorbed in a given time is governed by the volume of pulmonary blood flow. The entire period of rebreathing must be short enough that no appreciable recirculation of blood once exposed to the air in the rebreathing bag can occur; this recirculation may be a source of error in measurements made during periods of rapid circulation, that is, of exercise. Changes in circulation time due to variations in the condition of patients studied at intervals while in failure might also introduce errors. Another source of inaccuracy derives from the fact that it is sometimes difficult to obtain, in a short period, thorough mixing of the gas mixture being rebreathed in patients with changes in the lungs due to congestive failure (page 63) It is therefore necessary to prolong the rebreathing period, thereby increasing the possibility of recirculation of the blood. Still another source of inaccuracy in the acetylene method is the fact that small errors in analysis lead to large errors in results; it may not be possible to obtain duplicate determinations within less than plus or minus 10 per cent.

(*d*) *Ethyl iodide methods.* In these methods ethyl iodide consumption and arteriovenous difference are substituted for oxygen consumption and arteriovenous difference in Fick's formula The original ethyl iodide method of Henderson and Haggard (1925) yielded erroneous results because these authors disregarded the presence of ethyl iodide in the venous blood and incorrectly estimated the partition coefficient of that substance between air and blood. These errors were, however, constant, so that many authors believed the method to be useful. Starr and Gamble (1928) revised the method, eliminating many of the errors, but the results obtained in normal subjects are still well below those yielded by the use of catheterization of the heart.

Methods not based on the Fick principle.—The methods for measuring cardiac output that do not use the Fick principle were designed to avoid the criticism that methods based on exchange of gases in the lungs are fundamentally insecure because of the known impairment of pulmonary function in cardiac decompensation (page 53); all of these methods yield data that are of little value unless the oxygen consumption is measured at the same time.

(*a*) *Roentgenokymograph.* The output per cardiac beat is estimated by means of the roentgenokymograph (Keys and Friedell, 1939, LaDue and Fahr, 1943). Errors occur because of the fact that the heart is studied in only one plane and, consequently, changes in volume are estimated by means of formulas that may not be precisely applicable in given cases, especially where the contour of the heart is abnormal. Additional inaccuracies may arise because of the difficulty of defining the cardiac border and because changes in auricular size and shape may be included in the measurements. Moreover, regurgitant valvular lesions cause great errors. Unless many beats are studied, the effects of respiration may also introduce misleading variations.

(*b*) *Dyes* Dyes may be injected intravenously (Hamilton *et al*, 1932). In these methods the values obtained are calculated from ideal formulas and errors may be large. In certain cases, however, valid qualitative conclusions may be drawn from repeated measurements.

(*c*) *Pulse pressure and pulse-wave velocity* Methods which use changes in pulse pressure and pulse-wave velocity (Bazett *et al*, 1935, 1941) have not been widely used in studies on congestive failure Recent work of Remington *et al.* (1948) shows that such methods give erroneously high values in congestive failure, where values obtained by means of the catheter are low

(*d*) *Ballistocardiograph.* When the ballistocardiograph is used (Starr, 1941), errors may be introduced by failure to study a large enough number of beats and by the occurrence of marked changes in pulse rate; the method is unreliable in heart disease (Nickerson *et al.*, 1947).

Whatever may be the criticisms that can be leveled at one method or another, valid conclusions as to changes in cardiac output can be drawn if all the diverse methods yield results that are similar qualitatively. Such is fortunately the case in chronic cardiac decompensation.

Observations on cardiac output in congestive failure.—A large number of measurements of cardiac output or arteriovenous difference employing various methods have been recorded. In almost all instances the cardiac output was found to be low or the arteriovenous difference high (Bloomfield *et al.*, 1946, 1948; Howarth *et al.*, 1946; McMichael and Sharpey-Schafer, 1944, Merrill, 1946; Merrill *et al.*, 1946; Sharpey-Schafer, 1946; 1). In addition, studies of peripheral blood gases (page 70) yield comparable results A certain amount of overlapping occurs, however, when the cardiac outputs of normal subjects and decompensated patients are compared. This is not surprising, for in normal subjects Grollman (1929) found a spread of 30 per cent about the mean obtained by his method, and Donal *et al.* (1934) and Cournand *et al* (1945), using other methods, found a somewhat greater range of variation It is apparent that a low normal figure for cardiac output might actually represent a considerable decrease in the case of a patient for whom the normal value before the onset of congestive failure was at the upper limit of the normal range for all individuals. It must be borne in mind, moreover, that some types of cardiac decompensation may occur with a normal cardiac output. This situation obtains in diseases in which cardiac output is usually increased, namely, febrile diseases, anemia, beriberi, thyrotoxicosis, acidosis and arteriovenous aneurysm To this list has recently been added cor pulmonale (Richards, 1945, McMichael and Sharpey-Schafer, 1944, Sharpey-Schafer, 1946).

Eppinger and his co-workers (1925, 1927) found a normal or increased cardiac output in chronic cardiac compensation Their conclusions have been criticized on the basis of faulty technique and are now thoroughly discredited. Schoen and Derra (1930), using cardiac puncture, and Harrison *et al.* (1934) and McGuire *et al.* (1938, 1939*a*,*b*), who employed a modified Grollman acetylene method, found normal or even high cardiac outputs in some patients with cardiac decompensation. The data of Schoen and Derra (1930) are scanty and not presented in sufficient detail to permit analysis. The findings of Harrison *et al.* (1934) are seen on closer examination to conform to those of a majority of workers in this field. Many of the patients with more than minimal evidences of myocardial insufficiency who were studied by Harrison and his co-workers had low cardiac outputs and of ten with normal or almost normal values, all but one had

basal metabolic rates of from plus 15 to plus 78 per cent. A similar analysis may be made of the data of McGuire *et al.* (1938, 1939*a*,*b*). Obviously, the cardiac output in such cases cannot be compared with that of undecompensated individuals whose basal metabolic rate is within limits of plus or minus 10 per cent of the average normal. The importance of the relationship between cardiac output and oxygen consumption has been stressed by many authors (Davies and Gilchrist, 1927, Grollman, 1929; Krogh and Lindhard, 1912, Lindhard, 1918; Lundsgaard, 1916, Starr *et al.*, 1933). It is probable that, as Means (1924) suggested, a more precise relationship exists between carbon dioxide production by the body and the output of the heart. At any rate, it is apparent that the cardiac output in proportion to the body metabolism is low in patients with cardiac decompensation When exceptions to this rule are found, they may often be explained on the basis of such complicating factors as anxiety, anemia, arteriovenous aneurysm, elevated metabolic rate consequent to fever or thyroid disease, pregnancy, acidosis, thiamine deficiency or cor pulmonale.

It has been shown (Altschule and Gilligan, 1938) that even a small increase in venous pressure in normal man results in striking increases in cardiac output Patients with high venous pressure at rest consequent to congestive failure fail to exhibit this response, although McMichael (1938*a*) concluded that a partial response is present in cardiac patients who are only moderately decompensated. It may be concluded, however, that the output of the heart is always low relative to the venous pressure in chronic cardiac decompensation.

As a rule, diminution in cardiac output per beat is even greater than that in output per minute in cardiac decompensation, since some degree of tachycardia occurs in almost all patients with that syndrome. Even more marked deviations from the normal are found if the cardiac output per minute or per beat is compared to the cardiac size, as was pointed out by Nylin (1933), Lysholm *et al.* (1934), and by Starr and co-workers (1933, 1934).

The low cardiac output found in congestive failure is largely the consequence of myocardial weakness, but lessened negativity of intrapleural pressure (page 53) and auricular fibrillation or some other arrhythmia may be contributory factors (page 250). The contention of McMichael and Sharpey-Schafer (1944), that overstretching of

the heart consequent to greatly elevated venous pressure results in low output, has been criticized (Bloomfield *et al.*, 1947) and appears to be unsubstantiated by the data presented.

A decrease in cardiac work occurs in congestive failure, since the work of the heart is directly proportional to its output (Evans and Matsuoka, 1915) A number of studies of the efficiency—that is, the ratio of work performed to oxygen consumption—of the failing heart have been made on isolated heart or heart-lung preparations, and all show that the efficiency of the heart in failure is much reduced It is possible that this loss of efficiency has as its clinical counterpart the lengthening of the duration of electrical systole that occurs when the heart fails (Berliner, 1931, Cheer and Dieuaide, 1931, 1932; Geiger *et al*, 1941; Phang and White, 1943) Studies of cardiac efficiency in the intact animal have been reported (Harrison *et al*, 1936), but are open to criticism on technical grounds It has been suggested (Harrison *et al.*, 1936) that diminished cardiac efficiency rather than low output determines the presence or absence of congestive failure This is probably not the case, for it is difficult to understand how edema develops in the ankles, merely because the heart, located four feet distant, shows a low ratio of work output to energy input, that is, low efficiency, in patients with cardiac decompensation. Changes in cardiac dynamics can influence the tissues only through the cardiac output and the peripheral and pulmonary venous pressures, it must therefore be concluded that while cardiac inefficiency in failure is theoretically important, it is not directly responsible for the development of signs and symptoms of congestive failure

On the other hand, consideration of cardiac efficiency is essential for the understanding of some otherwise confusing matters. For instance, it is important to bear in mind the fact that under certain circumstances increases in cardiac output are harmful, whereas in others they are beneficial to patients with cardiac decompensation. Thus, increases in cardiac output brought about by anxiety, fever, effort, anemia, thyrotoxicosis, injection of epinephrine, and probably also the injection of aminophylline, are not associated with increased cardiac efficiency, accordingly, these conditions constitute a burden upon the heart and may precipitate or aggravate its failure Contrariwise, the increase in the output of the heart that occurs with digitalis (page 188) or during spontaneous recovery from failure is due to

basal metabolic rates of from plus 15 to plus 78 per cent. A similar analysis may be made of the data of McGuire *et al.* (1938, 1939*a*,*b*). Obviously, the cardiac output in such cases cannot be compared with that of undecompensated individuals whose basal metabolic rate is within limits of plus or minus 10 per cent of the average normal. The importance of the relationship between cardiac output and oxygen consumption has been stressed by many authors (Davies and Gilchrist, 1927; Grollman, 1929; Krogh and Lindhard, 1912, Lindhard, 1918; Lundsgaard, 1916; Starr *et al.*, 1933). It is probable that, as Means (1924) suggested, a more precise relationship exists between carbon dioxide production by the body and the output of the heart. At any rate, it is apparent that the cardiac output in proportion to the body metabolism is low in patients with cardiac decompensation. When exceptions to this rule are found, they may often be explained on the basis of such complicating factors as anxiety, anemia, arteriovenous aneurysm, elevated metabolic rate consequent to fever or thyroid disease, pregnancy, acidosis, thiamine deficiency or cor pulmonale.

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The low cardiac output found in congestive failure is largely the consequence of myocardial weakness, but lessened negativity of intrapleural pressure (page 53) and auricular fibrillation or some other arrhythmia may be contributory factors (page 250). The contention of McMichael and Sharpey-Schafer (1944), that overstretching of

Meakins *et al.*, 1923; Moore *et al.*, 1926; 2), with normal responses in only a few (Alt *et al*, 1930; Bansi and Groscurth, 1930*a*; Means and Newburgh, 1915; Newburgh and Means, 1915). McMichael (1938*a*) observed a normal response during light exercise and an abnormally small increase in cardiac output in heavier work. McGuire *et al.* (1939*b*) made a systematic study of patients in various stages of failure and found a smaller than normal increase in cardiac output in compensated patients during exercise and a still smaller rise in those in failure. Hickam and Cargill (1948) recently have provided excellent data, obtained by means of the catheter, which show that the cardiac output does not increase after exertion in patients with congestive failure.

The significance of an abnormally large arteriovenous oxygen difference after exercise (Bansi and Groscurth, 1930*b*, Harris and Lipkin, 1931; Weiss and Ellis, 1935) is the same as that of the aforedescribed data; Weiss and Ellis (1935) found almost complete deoxygenation of venous blood after exercise in some patients. All of these observations explain in part the abnormal rise in venous pressure (page 35), the marked lactic acidosis (page 86) and the large oxygen debt (page 91) of cardiac patients The rise in cardiac output during exercise, though smaller than normal, apparently lasts longer in cardiac patients, implying a need to discharge the abnormally large oxygen debt that occurs in such individuals. These data are in accord with the increased peripheral "flow debt" observed by Abramson *et al.* (1942) in cardiac patients after exercise.

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Chapter I — Section 1

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increased efficiency and is, therefore, no additional burden upon the heart, the heart can do more work with no increase in energy requirement.

Changes in cardiac output in recovery from congestive failure are variable Thus, if recovery is associated with increased myocardial strength, either of spontaneous occurrence or as a result of the action of digitalis (page 188), cardiac output rises If, on the other hand, improvement in signs and symptoms occurs as a consequence of the administration of oxygen or of diuretics, no increase in cardiac output need occur (page 192) Therefore, precise correlation between disappearance of signs and symptoms and changes in cardiac output is fundamentally impossible. An additional source of confusion lies in the fact that a marked fall in basal metabolic rate may occur during recovery from failure, so that the more or less parallel changes in cardiac output give the appearance of a decrease in the latter. Thus, in the data of Harrison *et al* (1934) many such instances of decreasing cardiac output in recovery occur, but actually this is more apparent than real, for in nine patients of ten studied by those authors the arteriovenous difference fell or did not change significantly; the cardiac output in these patients was unchanged or increased relative to the metabolic rate. The data of McGuire (1938, 1939*a*,*b*) may be analyzed in a similar manner

The lack of parallelism between fall in cardiac output and severity of signs and symptoms in congestive failure was noted years ago by Lundsgaard (1916) and has been stressed more recently by Harrison (1934, 1935), Starr (1941) and McGuire (1938, 1939*a*,*b*) The reasons why this correlation does not, and indeed cannot, exist will be discussed in various portions of this review.

Effects of exercise—The validity of methods used for measuring the cardiac output at rest has not been satisfactorily established for studies on exercising patients with cardiac decompensation. Accordingly, most data on the effects of exercise have been obtained in experiments on compensated or only mildly decompensated cardiac patients. The amount and type of work used as a test load by various investigators have varied so greatly that precise quantitative analysis of all the available data is difficult. Most authors describe an abnormally small rise in cardiac output in their patients compared to normal subjects performing the same task (McGuire *et al.*, 1939*b*;

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2. *Circulation Time*

The significance of the pulmonary circulation time was discussed in 1931 by Blumgart in his review of the subject. Since that time his observations have been corroborated and extended; various segments of the circulation may now be measured through the use of a variety of test substances. The arm-to-tongue, arm-to-face or arm-to-carotid-sinus time measures the circulation time in the antecubital and brachial vein, the superior vena cava, the right heart, the lungs, the left heart, and a short arterial segment. This may be divided into arm-to-lung time by the use of ether or paraldehyde, and lung-to-brain time by the use of inhalation of 15 to 25 per cent carbon dioxide. The arm-to-tongue, -face or -carotid-sinus time is long in almost all patients with cardiac decompensation (3). Blumgart (1931) stressed the relation between this sign of pulmonary congestion and another — diminution of the vital capacity — consequent to an increase in the amount of blood in the lungs. In recovery from congestive failure, both return to or toward normal.

Blumgart (1931) also pointed out that slowing of the circulation occurs in myxedema, not as a consequence of pulmonary congestion, but as a result of low cardiac output. Altschule and Volk (1936) showed that prolongation of the circulation time parallels reductions in cardiac output in individual patients with hypothyroidism, but that equivalent reductions in cardiac minute volume output in patients with pulmonary congestion are associated with much greater increase in circulation time than in patients without congestion. It may be concluded, therefore, that the slowing of the circulation through the lungs in cardiac decompensation is related to (i) the lowered cardiac output and (ii) the engorgement of the pulmonary vessels which occurs in that condition.

Slowing of the circulation, like diminution of the vital capacity, is frequently associated with dyspnea in patients with congestive failure; measurement of the circulation time is clinically useful in helping to distinguish between dyspnea consequent to cardiac decompensation and dyspnea due to pulmonary disease. Under some circumstances the circulation time may lie within the normal range in cardiac decompensation; this may occur when congestive failure oc-

curs in association with anemia, fever, pregnancy, arteriovenous aneurysm, thyrotoxicosis, severe anoxia, severe acidosis and thiamine deficiency. Exercise shortens the circulation time by the same number of seconds in normal subjects and in cardiac patients with long circulation times at rest (Cannon *et al.*, 1939), which suggests that an increase in pulmonary congestion does not occur in such patients during exertions. The observations of Gilbert and Goldzieher (1946) that insulin and adrenalin each increase the circulation time in decompensated cardiac patients but not in normal subjects are difficult to accept.

The carbon dioxide time is also increased in patients with congestive failure (Bornstein, 1912; Grubner *et al*, 1939). It is questionable whether this has any special significance, since it is not ascertainable how much of the elapsed time is occupied by the blood containing the inhaled carbon dioxide in passing through the pulmonary veins on the one hand and the left ventricle, ascending aorta and carotid artery on the other.

The ether time, which measures the venous segment of the circulation time, that is, the portion up to the lungs, is often used to diagnose "right heart failure." The ether time is often long in chronic cardiac decompensation (4, Hitzig, 1935), but is more often normal than is the arm-to-tongue time in patients with congestive failure (Baer and Slipakoff, 1938; Lian and Facquet, 1936, Miller, 1934). Hitzig *et al.* (1935) state that the ether time is normal in "left ventricular failure," but actually it is also not uncommonly normal in patients with edema, hepatomegaly and high venous pressure. Hitzig's (1935) observation that a close parallelism exists between elevated venous pressure and increased ether time is not corroborated by Hussey *et al.* (1942), Epstein and Young (1943), nor Motta (1937). The lack of parallelism between ether time, venous pressure and the presence or absence of edema and hepatomegaly puts any attempts to diagnose "right ventricular failure" on a most insecure basis (see also page 102).

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Nylin (1943, 1945*b*; Gernandt and Nylin, 1946) has adopted and developed the idea expressed earlier by David and Bouvrain (1940) that the increased circulation time of cardiac decompensation is a reflection of the accumulation of an increased amount of blood in the heart as a consequence of dilatation of the latter Nathanson and Elek (1947) have also espoused this concept. Nylin's statistical studies and those of Nathanson and Elek (1947), which show a parallelism between cardiac size and circulation time, do not, however, in themselves, establish a direct relation between the two. Similarly, results of Nylin's above-cited studies, which show delayed mixing of intravenously injected material in patients with cardiac decompensation, are explicable on the basis of the low cardiac output, slow blood flow, and large blood volume of congestive failure. Meneely and Chestnut (1947) have criticized Nylin in a similar vein. It is probable that the increased *cardiac* blood volume, which almost certainly occurs commonly in patients with heart disease, is of little direct importance in causing the manifestations of cardiac decompensation; it is also difficult to see how the stagnation of enough blood in the heart to slow the circulation time can occur with the heart beating 80 to 120 times a minute and expelling liters of blood during this time.

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3. *Peripheral Circulation. Temperature Regulation*

Peripheral Circulation.—Data on peripheral blood flow may be obtained by various methods. These include studies of the gases in samples of blood taken from peripheral vessels (page 70), plethysmographic methods (Abramson *et al*, 1942), and techniques based upon cutaneous temperature changes (Stewart *et al*, 1946). Marked changes in blood flow through the extremities are not to be expected in patients with congestive failure, since the flow through resting muscle is small (Holling, 1939) and that in the skin amounts only to a few hundred cubic centimeters per minute for the whole body.

Few direct measurements of peripheral blood flow in patients with congestive failure have been reported G. N Stewart (1912, 1914) noted decreased flow in the hands, varying roughly with the degree of failure, in cardiac patients Flow through the hands, however, is so strongly influenced by neurogenic factors which cannot always be

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congestive failure. It is significant that an increased "flow debt" also occurs when anoxia is induced in normal subjects who exercise while breathing low concentrations of oxygen (Abramson *et al.*, 1943*b*)

Temperature regulation—Slight to moderate elevation of body temperature in the absence of evidences of infection is frequently observed in patients with severe congestive failure Cohn and Steele (1934) studied this phenomenon and found a close parallelism between the presence of signs of marked failure and elevation of temperature, except that the latter might occur before the former became evident. Steele (1934) further reported that the difference between skin and rectal temperatures is abnormally great in cardiac patients, a finding not corroborated by Stewart *et al.* (1946); however, Stewart's patients had elevated metabolic rates and in proportion to the increase in heat production their cutaneous temperatures were low. Both Steele (1935) and Burch (1946*a*,*b*) observed that such patients eliminate two or three times as much heat as normally via the lungs.

These findings are not unexpected in view of the known marked reduction in peripheral blood flow (page 27) and the vasoconstriction (page 32) which ordinarily occur in severe failure Diminution in blood flow to the periphery necessarily affects the dispersal of heat generated within the body, thereby giving rise to an elevation of body temperature Steele (1937) was able to reproduce these conditions in normal subjects by slowing the peripheral circulation by means of tourniquets applied to the extremities. He suggested (1934) that this inability to disperse heat normally via the skin might be one cause of the hyperpnea exhibited by patients with cardiac decompensation. This view is supported by the clinical observation that many patients with severe congestive failure claim to experience increase of dyspnea when wrapped in blankets or placed in a warm, stuffy room (Burch, 1946*c*). It should be noted that other heat-dispersing mechanisms, namely, water loss through the skin and sweating in response to heating, are also impaired in patients with cardiac decompensation (Burch, 1946*c*; Kauf and Zak, 1927). D'Alton *et al.* (1948) found no diminution in sweating at ordinary temperatures

controlled as to make these data of little value in themselves. H. J. Stewart (1946) found values that were in the normal range but low in relation to the elevated metabolic rates exhibited by his patients. On the other hand, the low oxygen content of the antecubital and femoral venous blood found by most observers in decompensated cardiacs show that the volume of flow is reduced in congestive failure (Harrop, 1919; Landt and Benjamin, 1941; Lundsgaard, 1918*a*,*b*,*c*; 5); Holling (1939) has demonstrated a parallelism between venous oxygen content and blood flow. The wide arteriovenous differences for carbon dioxide found in peripheral bloods by Pearce (1917, 1921) and Scott (1919) also indicate slow peripheral flow. In addition, the results of direct microscopy (page 47) also prove that the speed of flow is reduced.

Harrison and Pilcher (1929) concluded from their studies of blood gases that edema in cardiac patients causes an increase in the flow through the edematous areas, but their conclusions have been severely criticized by Weiss and Ellis (1935), who used the same methods. Abramson *et al.* (1943*a*) used a plethysmographic method, and also found evidence of increased flow through edematous limbs; however, some error in their method is suggested by the fact that it recorded increased flow in the presence of venous occlusion, whereas Friedland *et al.* (1941), who also used a plethysmographic method, found that venous stasis decreased blood flow through an extremity. The nature of the error in Abramson's work is probably elucidated by the observations of Wilkins and Bradley (1946), who found that the application of the cuff as required in plethysmographic methods might result in a temporary increase in blood flow if the latter was low initially Rocchini (1937), who used fluorescein in his studies, claimed that the circulation through the edematous limbs of cardiac patients is slower than that through limbs free of edema. It is probable that edema has in itself no specific effect on blood flow.

During exercise the peripheral blood flow fails to increase in a normal manner and venous blood becomes markedly deoxygenated in patients in failure (Harris and Lipkin, 1931; Weiss and Ellis, 1935). Even in compensated cardiac patients the blood flow remains elevated longer after exercise than in normal subjects (Abramson *et al.*, 1942), implying an attempt to discharge an abnormally large oxygen debt; presumably a still larger "flow debt" would occur in the presence of

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4. *Arterial Blood Pressure. Peripheral Resistance. Vasoconstriction*

The arterial blood pressure shows no consistent change as a consequence of congestive failure, although a fall is often described in recovery (Seymour *et al*, 1942, 6) This decrease in arterial pressure is difficult to interpret, since some lowering of blood pressure usually occurs when hypertensive patients and some normal subjects remain in bed over a period of some days. It is probable that cardiac decompensation has *no consistent effect on arterial blood pressure; any* tendency toward a fall consequent to lowered cardiac output is likely to be counteracted by vasoconstriction caused by sympathetic activ-

ity, the latter precipitated by anoxia, anxiety or discomfort. The work of Henry *et al* (1947) shows that vasoconstriction occurs in the extremities in normal subjects exposed to anoxia. Evidence of vasoconstriction is afforded not only by the pallor the patients exhibit but also by the fact that reactive hyperemia is diminished (von Marsovsky, 1942). This cutaneous vasoconstriction may at times lead to a false diagnosis of shock. Renal vasoconstriction also occurs (Merrill, 1946; Merrill *et al*, 1946) Since the cardiac output is low in decompensation and the arterial pressure is normal or slightly elevated, is is clear that the total peripheral resistance must be increased (Seymour *et al.*, 1942, Richards, 1945, Stead *et al.*, 1948; Bloomfield *et al.*, 1948), which is additional evidence of vasoconstriction; the resistance falls to or toward normal in recovery (Seymour *et al.*, 1942) The reported finding of renin (Merrill, 1946; Merrill *et al*, 1946) in the renal venous blood in congestive failure may be important for an understanding of changes in blood pressure, although the amounts reported to be found are so large as to arouse skepticism

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5. *Venous Pressure. Venous Tone*

Venous engorgement is one of the cardinal signs of congestive failure. Measurements of the venous pressure by many workers, by direct or indirect methods, have corroborated this clinical finding (Gaertner, 1903; Clark, 1915; Eyster, 1926; Winsor and Burch, 1946; 7). Most of these authors agree that the venous pressure is normal in patients with organic cardiac disease but without signs or symptoms of failure (exclusive of tricuspid disease and pericarditis), but Gaertner (1903) and Clark (1915) found it to be elevated in some such patients. A considerable degree of overlapping of venous pressure values may be found when normal individuals, compensated cardiac patients and patients in failure are studied (Altschule, 1938; 8). When patients with congestive failure and high venous pressures sit up, the pressure in the veins falls, a phenomenon which does not occur in normal subjects (Winsor and Burch, 1946); the importance of this finding in regard to the genesis of orthopnea is apparent. A single observation records the fact that tone of the small veins is normal in patients with elevated venous pressure (Capps, 1936).

The normal response to an increase in venous pressure is an increase in cardiac output (Altschule and Gilligan, 1938); decompensated patients who show increased venous pressure at rest have diminished cardiac outputs.

The rise in venous pressure frequently found in cardiac decompensation is due in part to the inability of the heart to take up and propel forward all the blood brought to it. This conclusion is supported by the loss of gradient between venous and right auricular pressures in chronic failure (page 45) and also by the striking and almost immediate rise in venous pressure which often occurs in patients with paroxysmal arrhythmias and rapid ventricular rates (page 251); vasoconstriction may, however, play a part in the latter phenomenon. The fact that the rise of venous pressure that follows exercise is greater and more prolonged in cardiac patients than in normal subjects (9, Schott, 1912. Harrison *et al.*, 1932; White *et al.*, 1925) also suggests the importance of impaired cardiac output; the increased venous return consequent to the pumping action of the exercising muscles is more than the weakened heart can propel forward. It is to be noted, however, that even in normal subjects exercise in the anoxic state which occurs at high altitudes is associated with a greater than normal rise in venous pressure (Schneider, 1916); it is not unlikely, therefore, that excessively labored breathing also brings about elevated venous pressure. Pulmonary congestion causes changes within the lung which result in increased intrapleural pressure (page 53), the latter change impedes the entrance of blood into the thorax (Hooker, 1914; Holt, 1943, 1944; Prinzmetal and Kountz, 1935), thereby tending to increase the venous pressure.

Still another factor making for a rise in venous pressure is increased blood volume. Several authors (Brandt, 1931; Wollheim, 1931, Gibson and Evans, 1937; Warren and Stead, 1944) who measured both have stressed the parallelism between the two in cardiac decompensation (page 6), and Starr (1940) reached the same conclusion by showing that after death the "static" pressure in the body of a decompensated cardiac patient is much above normal. Starr and Rawson (1940) studied the effects of lowered outputs in a model circulation and likewise found that the rise in venous pressure was related to an increase in the volume of fluid in the circulation. The work of Gibbons (1948) and of Threefoot, Gibbons and Burch

MERRILL, A. J., L. J. MORRISON, and E. S. BRANNON, Concentration of renin in renal venous blood in patients with chronic heart failure, *Am. J. Med.* 1, 468 (1946)

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(1947) shows that no regular temporal relation exists between increase in body weight and rise in venous pressure.

When the venous pressure is elevated in cardiac decompensation, it usually falls to or toward normal in recovery. Indeed, it often begins to decrease shortly after the patient is put to bed (Hussey, 1936), before the action of more specific therapy becomes effective. This phenomenon may be merely the consequence of relaxation, for straining raises the venous pressure (Meyer and Middleton, 1929; Liedholm, 1939, Adams, 1939, Chapman and Linton, 1945; Hamilton *et al.*, 1944). Among the procedures that rapidly lower venous pressure are venesection (page 227), application of tourniquets to the extremities (page 224) and, in patients with pleural effusion, thoracentesis (page 334) The bearing of these findings on the relief of orthopnea and edema will be discussed in another place (page 156) Failure of the venous pressure to fall or a continuous rise during treatment may be a poor prognostic sign An elevated venous pressure is found occasionally before dyspnea appears and often before edema and orthopnea become manifest. In many instances, however, marked signs of failure, such as râles in the chest, cyanosis, hepatic engorgement or even edema may be present without any elevation of venous pressure above the upper limit of the normal range (Winsor and Burch, 1946).

In addition to studies of the effects of exercise on venous pressure cited above, other procedures employing measurement of pressure in the veins have been suggested as tests of cardiac function. They are, however, difficult to interpret and therefore of doubtful value. These tests include the Valsalva maneuver (Meyer and Middleton, 1929; Liedholm, 1939), coughing (Lauson *et al*, 1946), and sudden occlusion of both femoral arteries (Chiorazzo and Perini, 1938); abnormal responses are said to occur in patients with congestive failure. The finding of Gilbert and Goldzieher (1946) that epinephrine and insulin raise venous pressures in cardiac patients but not in normal subjects is clearly an error.

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6. *Right Auricular and Right Ventricular Pressures*

The right auricular pressure is high in congestive failure (McMichael and Sharpey-Schafer, 1944; Richards, 1945, Bloomfield *et al*, 1946; 10) and the normal gradient between venous and intra-auricular pressure falls markedly, usually to an unmeasurably low value This finding appears to be conclusive evidence of back pressure from the heart. The high pressure within the heart is, however, due in part to increases in intrapleural pressure which may occur in cardiac decompensation (page 53), for the intra-auricular pressure varies with the intrapleural pressure (Bloomfield *et al.*, 1946). More important probably as the cause of high right auricular pressure is the increase in right ventricular pressure that occurs (Bloomfield *et al.*, 1947, Cournand *et al*, 1944, Richards, 1945; Battro *et al*, 1949; Hickam and Cargill, 1948) Back pressure from the engorged pulmonary vessels leads to a rise in systolic intraventricular pressure only, to judge from the results of studies in patients with mitral stenosis (Bloomfield *et al*, 1946). However, when the heart fails, both systolic and diastolic pressures are elevated, a finding that suggests vasoconstriction in the pulmonary circuit Recent work by Motley *et al* (1947) indicates that anoxia causes marked pulmonary vascular constriction It is to be noted (page 32) that the peripheral arterial tree also shows evidence of constriction in patients with chronic cardiac decompensation.

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7. *Cutaneous Capillaries. Capillary Pressure*

Engorgement of the tissue capillaries, often to the point of hemorrhage, is the usual postmortem finding in congestive failure. The degree of congestion that exists during life in such patients cannot be estimated accurately from the sections of fixed tissues, since some of the changes may be agonal or postmortem. Direct observation of the capillaries of the nail folds of patients with congestive failure has been possible for many years, and the findings of all observers (Crawford, 1926, 1927; **11**) are in substantial agreement. The visible capillaries are increased in number, consistently show dilatation of the venous limb and may exhibit slight narrowing of the arterial limb. The blood in them is dark, moves slowly and may be motionless for abnormally long periods of time; the column of moving blood often appears granular or segmented. It is to be noted also that the small venules of the subpapillary region are likewise abnormally numerous and prominent. Hisinger-Jägerskiold (1923) found these changes only in patients with peripheral failure and not in those in whom the signs of congestion were limited to the lungs; the latter patients showed only cutaneous capillary constriction. The reason for the dilatation of the venous limb of the capillaries is made clear by the observations of Krogh (1929) and of Landis (1928), who showed that anoxemia causes capillary dilatation. In congestive failure the effects of anoxemia are naturally most marked at the venous end of the capillary.

It is to be expected that the capillary pressure will always be higher than the venous, so that a finding of elevated venous pressure carries with it the implication in general that the capillary pressure is also elevated, as direct measurements show (Eichna and Bordley, 1939, 1942). Earlier measurements of capillary pressure in patients with congestive failure by indirect methods gave variable results (Meldolesi, 1926; Boas and Dooneief, 1924); these methods are demonstrably inaccurate (Eichna and Bordley, 1939) More recently measurements have been made by means of direct micro-injection of the cutaneous capillaries in patients in failure. Those with edema were observed to have high values (Fahr and Ershler, 1938, 1941), while those without edema had capillary pressures within the normal

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range. High pressures fell to normal in recovery, according to these authors However, their finding that the capillary pressure may be found to be abnormally high, even when the venous pressure was not outside the normal range, invites skepticism.

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9. *Lung Volume. Pulmonary Elasticity and Distensibility. Intrapleural Pressure*

Many authors, chiefly clinicians, have ascribed the dyspnea of heart disease to a reduction in vital capacity As Christie and Meakins (1934) have emphasized, this erroneous concept is based on loose thinking consequent to lack of appreciation of the significance of the various subdivisions of the total lung volume. It is, therefore, essential to understand clearly the terminology bearing on this subject.

Harrison (1933, 1934) observed improvement in orthopnea in most instances after spinal drainage; he reported (1934) that the peripheral venous pressure also usually decreased significantly after this procedure. The observation that respiratory distress is relieved by removal of spinal fluid has been corroborated by others (Altschule, 1933; Volini and Levitt, 1940) Robertson and Fetter (1935) felt that withdrawal of spinal fluid performed simultaneously with venesection was more effective in relieving orthopnea than was the latter alone Harrison (1934), however, was unable to correlate the relief of orthopea with lowering of the venous pressure in his patients, and felt that orthopnea was due to increased intracranial pressure. Patients with increased intracranial pressure due to primary intracranial disease do not have dyspnea or orthopnea, however, nor does lumbar puncture alter their respiratory dynamics in any consistent manner.

The reason for the temporary relief of respiratory distress in congestive failure after spinal puncture is probably a transitory increase in blood flow through the cerebral respiratory centers; high intracranial pressure has been shown to cause a decrease in cerebral blood flow in man (Shenkin *et al*, 1946). The reason for the reported decrease in peripheral venous pressure following spinal puncture is obscure.

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1923), where it may be decreased significantly. Accordingly, it appears that, with possible exceptions in patients with very severe failure, the space available for breathing is not decreased.

Reported measurements of the *residual* air are also numerous (**14**) but many are unacceptable. The more reliable data of Binger (1923), Christie and Meakins (1934), Kaltreider and McCann (1937), Poli (1938*a*,*b*) and Altschule *et al* (1943) shows that the residual air is usually increased in patients with chronic congestive failure, although Binger (1923) found that it might be decreased in severe failure; increase in residual air indicates that a state of mild secondary pulmonary emphysema is common in myocardial insufficiency.

All authors agree that the *reserve* air is reduced in this condition (Binger, 1923, Christie and Meakins, 1934, **15**) This finding indicates a loss of elasticity, which actually has been demonstrated by more direct methods as well (Christie and Meakins, 1934; Christie and McIntosh, 1934, Paine, 1940). The loss of elasticity, together with generalized muscular weakness, serves to explain the reduced expiratory velocity and pressure manifested by cardiac patients (Gross, 1943, Plotz, 1947, Heyer, 1946) The diminution in reserve air is paralleled by changes in the intrapleural pressure, the latter becoming less negative (Christie and Meakins, 1934, Christie and McIntosh, 1934; Paine, 1940), the conclusion of Poli (1936, 1938*a*, *b*) that it becomes more negative cannot be accepted. The loss of most or all of the intrapleural negative pressure impairs the effectiveness of inspiration and also impedes venous return; the latter change tends to elevate peripheral venous pressure (page 35).

The *complemental* air is diminished—often markedly—in chronic congestive failure (Binger, 1923, Siebeck, 1910; **16**) Accordingly, the distensibility of the lungs must be greatly impaired because of increased rigidity, as has indeed been demonstrated by more direct methods (Christie and Meakins, 1934, Christie and McIntosh, 1934). This in itself makes inspiration more difficult and also limits the increase in tidal air volume that normally occurs in response to work (page 62).

The vital capacity (Peabody and Wentworth, 1917, Rubow, 1908; Siebeck, 1910, **17**) and total capacity (**13, 14**) are both diminished, since both are derived from the reserve and complemental airs, the vital capacity entirely and the total capacity largely.

Functional residual (subtidal) air is the volume of air remaining in the lungs after normal expiration. It is the sum of the residual and reserve (supplemental) airs, and is largely a measure of the space available for respiratory exchange, it must be changed by mixing with and diffusion from the tidal air. A subdivision of the total lung volume having approximately the same significance is the *mid capacity*, a measure used by some continental authors; it consists of the functional residual air plus half the tidal air volume.

Residual air is the volume of air remaining in the lungs after maximal forced expiration.

Reserve (supplemental) air is the air which, after normal expiration, is expelled by maximal forced expiration. It is a measure of the elasticity of the lungs and in individual subjects varies with the intrapleural negative pressure, decreasing as the pressure approaches the atmospheric.

Complemental air is the air which, after normal expiration, is taken in by maximal forced inspiration, and is therefore a measure of the expansibility of the lungs and of the thoracic cage.

Vital capacity is the sum of the reserve and complemental air volumes and, since it measures both at the same time, may have no precise significance in some circumstances.

Total capacity is the sum of the residual, reserve, and complemental air volumes

Some of these subdivisions of the lung volume are measured easily and with accuracy, these include the reserve and complemental airs and the vital capacity. On the other hand, the residual and functional residual airs are measured by means of fairly complicated techniques, some of which do not yield accurate data in subjects in whom mixing in the lungs is impaired, including patients with cardiac decompensation

Although a number of authors have measured the functional residual air and the mid capacity in patients with congestive failure (13), the data in most instances are not acceptable, having been obtained by the use of methods that do not give accurate results in patients with abnormal lungs. The more reliable data of Binger (1923), Christie and Meakins (1934), Poli (1938*a*,*b*) and Altschule *et al.* (1943) indicate no great change in functional residual air in chronic congestive failure, except possibly in severe decompensation (Binger,

1923), where it may be decreased significantly. Accordingly, it appears that, with possible exceptions in patients with very severe failure, the space available for breathing is not decreased.

Reported measurements of the *residual* air are also numerous (**14**) but many are unacceptable. The more reliable data of Binger (1923), Christie and Meakins (1934), Kaltreider and McCann (1937), Poli (1938*a*,*b*) and Altschule *et al.* (1943) shows that the residual air is usually increased in patients with chronic congestive failure, although Binger (1923) found that it might be decreased in severe failure; increase in residual air indicates that a state of mild secondary pulmonary emphysema is common in myocardial insufficiency.

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The vital capacity (Peabody and Wentworth, 1917; Rubow, 1908; Siebeck, 1910, **17**) and total capacity (**13**, **14**) are both diminished, since both are derived from the reserve and complemental airs, the vital capacity entirely and the total capacity largely.

The mechanisms underlying the aforementioned changes in the lungs have been studied in experiments on animals by Romanoff (1911), Drinker, Peabody and Blumgart (1922) and Mack *et al.* (1947). The first two showed that congestion causes encroachment by the engorged vessels on the air spaces, thus supporting von Basch's earlier theoretical analysis Increased rigidity of the lung was also found by Romanoff (1911) and by Mack *et al.* (1947); that engorgement with blood increases the rigidity of tissues is well known

Attempts to correlate vital capacity with severity of dyspnea obviously cannot succeed, since many mechanisms participate in the genesis of that symptom, indeed, as a symptom, dyspnea is not measurable Similarly, the use of various ratios, such as respiratory minute volume to vital capacity (Harrison *et al.*, 1931, 1932), maximal respiration to vital capacity, maximal tidal air to vital capacity, or vital capacity to total capacity, is not valid. The ratios of residual air to total capacity and of functional residual air to total capacity have also been employed. All of these ratios are objectionable because there is no way in which the cerebral cortex of the dyspneic patient becomes aware of them, whereas abnormality of one of the factors previously discussed might make its presence known by lessened efficiency of breathing or by changes in blood gases The data of all authors show a great deal of overlapping of values for vital capacity in the dyspneic and nondyspneic groups of cardiac patients McMichael (1939) found a better correlation between the degree of hyperventilation and fall in cardiac output than between the former and decrease in vital capacity.

The validity of the application of methods for measuring the residual air to exercising patients has not been established; the vital capacity can, however, be measured during or immediately after exercise. Although a number of authors have described a slight reduction in vital capacity in normal subjects during severe exertion (18), Levine and Wilson (1919), Harrison *et al.* (1932) and Iglauer and Altschule (1938) found only insignificant changes, which the last named ascribed to difficulty in holding the breath long enough for performing maximal inspiration and expiration while dyspneic. All measurements of vital capacity in cardiac patients made dyspneic by exertion reveal no change from the control values (Alt *et al.*, 1930;

Harrison *et al.*, 1932). These findings strongly suggest that exertion causes no increase in pulmonary congestion.

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only 30 per cent. Actually, however, since somewhat more than 100 cc. of inspired air is used to wash out the airways that do not function in respiratory exchange, the figures for effective tidal air would be less than 400 cc. in the normal and 250 cc. in the decompensated state, a difference of 40 percent or more. The increase in respiratory minute volume at rest is therefore more apparent than real, and in many instances the *effective* minute volume respiration must be smaller or at least no larger than normal Expiration is prolonged (Thiel, 1930; Gross, 1943; Heyer, 1946; Plotz, 1947) and the velocity and pressure of expiration are low Shallowness of respiration in congestive failure is the consequence of several factors. (i) Increased rigidity of the lungs makes inspiration more laborious and prolongs expiration; the latter is normally purely passive, but in some cardiac patients active muscular effort is required. (ii) The lessened negativity of the intrapleural pressure which obtains in chronic cardiac decompensation makes inspiration less effective (iii) The diaphragm is often flattened in congestive failure, so that its excursions are limited. (iv) Reflexes from the congested lung and elsewhere may cause rapid shallow respiration (page 67). (v) The movements of the diaphragm may be limited by pleural effusions or abdominal distention. Accordingly, it is to be expected that factors that normally might increase tidal air volume, such as anoxia (Graybiel *et al.*, 1937) or hypercarbia (Peabody, 1915, 1917), will, in decompensated cardiacs, act largely by increasing the rate instead, as these authors have shown.

Effect of exercise.—The respiratory rate shows a greater than normal rise during exercise in cardiac patients (Kaltreider and McCann, 1937, Bendixen, 1931; Dennig and Prodger, 1933; Engelhard, 1927, Harrison *et al.*, 1932), as does the respiratory minute volume also (Campbell, 1934; Cullen *et al.*, 1931; Nielsen, 1937; Peabody and Sturgis, 1922; 23); both return to normal after cessation of exercise more slowly than normal The increase in respiratory minute volume is far in excess of the rise in oxygen consumption consequent to work, so that the ratio of respiratory minute volume to oxygen consumption, which is high in cardiac patients at rest, becomes larger (Herbst, 1928, Kaltreider and McCann, 1937, Knipping and Moncrieff, 1932; Zaeper *et al.*, 1939). The increase in minute volume respiration that occurs is largely the result of a rise in rate,

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10. *Respiratory Dynamics. Mixing in the Lungs*

The earliest clinical evidences of congestive failure are in most instances associated with altered respiratory dynamics during exertion; as the severity of decompensation becomes more marked, these changes become apparent even when the patient is at rest.

The alterations of pulmonary function that occur in moderately or severely decompensated cardiac patients at rest include increased respiratory rate (Campbell, 1934; Harrison *et al.*, 1932, Peabody, 1917, **19**) and respiratory minute volume (Beddard and Pembrey, 1908; Espersen, 1941, McMichael, 1939; **20**). Oxygen consumption is often increased in patients with cardiac decompensation (page 144), but the increase in respiratory minute volume is proportionately greater, often very much so (Herbst, 1928; Jansen *et al.*, 1932; **21**). Respiration is usually found to be shallow (Campbell, 1934; Knipping *et al.*, 1932*a*, *b*; Peabody, 1917; **22**), although Boyer and Bailey (1943) found it normal in depth and Thiel (1930) described it as increased. The shallowness of the respiration is reflected in the low carbon dioxide content of expired air (Barr and Peters, 1920, Boyer and Bailey, 1943; Campbell and Poulton, 1927).

The decrease in tidal air volume is really more serious than the measurements indicate. For instance, a patient whose tidal air volume is normally 500 cc. and in whom it falls to 350 cc. during a period of decompensation apparently has a decrease in tidal air of

mally great respiratory response to exercise. Actually, however, the degree of increase in respiratory minute volume in decompensated cardiacs far exceeds that which occurs when patients with severe pulmonary disease exercise, so that other factors must be more important. The absence of further increase in circulation time (page 19) and of additional decreases in vital capacity in exercising cardiac patients (page 54) suggests that increased congestion of the lungs does not occur. It is doubtful whether increased activity of reflexes from congested lungs during exertion is of importance, since the lungs do not appear to become more congested. Nor do reflexes arising in the great veins appear to be a factor (page 68). The large and persistent increase in respiration on exercise in congestive failure strikingly resembles the high and long curve of rise in blood lactic acid level which also occurs (page 86), the lactic acidosis is due to both arterial anoxia and lowered cardiac output. The importance of anoxia in the exertional hyperventilation of congestive failure is emphasized by the fact that patients with this disorder when made anoxic at rest hyperventilate more than do normal subjects under the same conditions (Graybiel *et al.*, 1937, Landt and Benjamin, 1941). In addition, even normal subjects hyperventilate abnormally when performing work under anoxic conditions (Clark-Kennedy and Owen, 1926; Asmussen and Chiodi, 1941) Impaired dispersal of the excess heat produced during exertion may be an additional factor causing increase in respiration.

Mixing—A number of authors record the fact that mixing in the lungs is abnormal in cardiac patients (Bruns, 1910, Siebeck, 1912) However, this function may in some instances be normal (Cournand *et al.*, 1941).

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for decompensated patients show a marked limitation of the degree to which the tidal air can increase during exercise (Bendixen, 1931; Campbell, 1934; Campbell and Sale, 1927, Dennig and Prodger, 1933, Kaltreider and McCann, 1937). Bendixen (1931) claimed that the ratio of maximal tidal air to vital capacity was normal in exercise in congestive failure, suggesting that the restriction of tidal air in exercise was merely a reflection of a lessened vital capacity. However, Campbell (1934) found it larger, and Engelhard (1927) smaller, than normal, so that attempts to attribute the lowered tidal air volumes of exercise in cardiacs solely to reduction of the vital capacity do not appear to be warranted. Increased rigidity of the lungs (page 53) explains the limited increase of tidal volume during exercise in cardiac patients in failure, the activity of reflexes arising in congested lungs and causing rapid shallow respiration does not appear to increase during exercise, but such reflexes may originate elsewhere. The maximal possible ventilation is of course considerably decreased in decompensated cardiacs (Jansen *et al*, 1932; Battro and Labourt, 1943; de Carrasco and Vorwerk, 1936; Engelhard, 1927), thereby limiting their activity greatly, for the difference between their high respiratory minute volumes at rest and their low maximal respiratory volume is small, that is, the "ventilation reserve" is low

Cardiac patients with more severe degrees of dyspnea usually have a larger respiratory minute volume at rest and on exertion than those in whom dyspnea is less marked, but the correlation is poor. In general, the increase in respiratory minute volume which occurs at rest or during exertion in congestive failure is associated with the feeling of shortness of breath, but it does not explain the sensation of dyspnea; when increases of respiratory minute volume comparable to those observed in congestive failure are induced in normal subjects by exertion or inhalation of carbon dioxide, the subjects do not become dyspneic (Harrison *et al*, 1931; Peabody, 1917)

The abnormally great increase in respiratory activity manifested during exercise by decompensated cardiac patients may be consequent to a number of factors Authors who ascribe dyspnea entirely to pulmonary congestion relate the increased respiration of cardiacs during exertion to the changes in the lungs, and point to the fact that patients with primary pulmonary disease also have an abnor-

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11. *Reflexes from the Lungs and Great Veins*

Drinker, Peabody and Blumgart (1922) found that congestion of the lungs induced in animals by clamping the pulmonary veins was associated with an immediate increase in respiratory rate. Underhill (1921) and Haggart and Walker (1923) also noted immediate increases in respiration when branches of the pulmonary artery were ligated, even though no change in cardiac output occurred, a marked increase in pulmonary arterial pressure was noted in these experiments. All of these results suggest that the respiratory changes observed might have been consequent to some reflex from the pulmonary vascular bed The fact that such reflexes exist was not, however, established until 1929, when Churchill and Cope (1929) reported experiments in which engorgement of the pulmonary vessels was induced in a lung completely isolated from the body except for its

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fusions in normal man may distend the veins greatly without giving rise to dyspnea or hyperpnea (Altschule and Gilligan, 1938; Altschule, Gilligan and Zamcheck, 1942).

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nerves. These observers clamped the artery and vein to that lung and then injected varying amounts of fluid into the pulmonary vessels; rapid shallow respiration resulted, which could be terminated by withdrawal of the injected fluid. The results of these experiments were corroborated by Schwiegk (1935), Harrison and his co-workers (1932, 1934) and Daly *et al* (1937), who also showed that the response was abolished by section of the vagus nerve. It seems to be fairly well established, therefore, that rapid engorgement of pulmonary vessels may give rise to changes in respiration by means of a reflex arc through the vagus nerve Whether this reflex remains active during long periods of continuous stimulation is not known.

It has been supposed for many years that the abnormal rigidity of the lungs that develops in patients with congestive failure is in itself a cause of dyspnea or at least hyperpnea Many authors have expressed the belief that this impaired collapsibility of the lungs activates the Hering-Breuer reflex, thereby causing rapid shallow breathing This point of view has been stressed chiefly by Christie (1938). Recent work in animals by Bülbring and Whitteridge (1945) appears to negate this concept, although other work supports it (Larrabee and Knowlton, 1946). It is impossible at present to arrive at a definite conclusion regarding the role of the Hering-Breuer reflex in the respiratory disturbances of cardiac decompensation.

The role of reflexes from the lungs in the genesis of dyspnea and hyperpnea of congestive failure is difficult to evaluate in general. That they are important in causing the respiratory manifestations associated with rapidly developing engorgement and edema in acute pulmonary edema seems to be established (page 61). In chronic cardiac decompensation, however, there is no certainty as to the part they play in dyspnea at rest The *increased* dyspnea of exertion does not appear to depend on pulmonary reflexes, for there is no evidence that *increased* congestion of the lungs occurs during exercise (page 63).

Distention of great veins was described by Harrison, Harrison *et al.*, (1932*a*, *b*) as a cause of reflex hyperventilation, but their experiments in animals have been criticized because slowing of the circulation through the brain probably also occurred The results of Megibow *et al* (1943) similarly do not establish the role of such mechanisms in dyspnea. The administration of large intravenous in-

would constitute an additional source of strain in patients with hearts already damaged. Moreover, it appears that the respiratory center in cardiac patients in failure is hypersensitive to oxygen lack (Landt and Benjamin, 1941; Graybiel *et al*, 1937) and therefore small changes in arterial blood oxygen saturation should aggravate dyspnea Additional evidence of the importance of the apparently mild degree of arterial anoxemia that occurs in cardiac decompensation is afforded by data on the effects of oxygen therapy Relief of symptoms, when it occurs, is usually associated with an elevation of the level of arterial blood oxygen saturation to or toward normal (Barach and Richards, 1931; Barach and Woodwell, 1921*a*, Cohn *et al*., 1932; Richards and Barach, 1934; Schoen and Derra, 1930); venous blood oxygen content also rises (Barach and Woodwell, 1921*a*).

Pulmonary factors are for the most part responsible for lowered arterial blood oxygen saturations in patients with cardiac decompensation not associated with congenital heart disease These factors include inefficient respiration, impaired mixing in the lungs, edema of the alveolar walls and, in some instances of severe mitral stenosis, organic changes in the alveoli (page 285). Tachypnea, of whatever origin, may also lower the arterial blood oxygen saturation (Meakins, 1920, 1922; Meakins and Davies, 1920, Barach and Woodwell, 1921*b*).

The strikingly low oxygen content of the peripheral venous blood in chronic congestive failure has been known for several decades and has been observed by many authors (Harrop, 1919; Lundsgaard, 1918*a*,*b*,*c*; 27); Harrison and Pilcher (1929) found no deviation from the normal. Low jugular venous blood saturations were found by McMichael (1939), Himwich and Fazekas (1944) and Raab (1931). The lowered venous blood oxygen levels are consequent to decreased cardiac output relative to the oxygen consumption of the tissues During exercise the inability of the cardiac output to increase in proportion to the increased needs of the body (page 8) results in a further fall in oxygen content of the venous blood, this is particularly striking in the exercising limb, where the levels may approach zero (Weiss and Ellis, 1935).

The fall in venous blood oxygen is more constantly found and more marked than in the arterial blood oxygen; consequently the arteriovenous oxygen difference is increased The venous blood oxygen

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12. *Arterial and Venous Blood Oxygen. Arteriovenous Oxygen Difference*

Many observers who have studied the arterial blood oxygen saturation in patients with chronic cardiac decompensation (Harrop, 1919; 21) report values that are somewhat below normal in some or many of their patients; a few describe consistently normal values (Eppinger *et al.*, 1926, 25). When a diminished arterial oxygen saturation occurs in uncomplicated congestive failure, the values usually lie above 85 per cent. During exercise little or no change in arterial blood oxygen saturation occurs in patients with cardiac failure (Himwich and Loebel, 1927; Cullen *et al.*, 1931; Eppinger *et al.*, 1926); patients with severe pulmonary disease usually show a fall. The decreases in saturation below the normal lower limit of 91 per cent which are found in patients with cardiac decompensation, though apparently small, are of importance, since they occur in a portion of the dissociation curve where small changes in saturation are associated with large changes in tension. In normal individuals the circulatory response to anoxia is increased cardiac output and more rapid blood flow (Asmussen and Chiodi, 1941; Davis, 1914, 26) in all parts of the body except possibly the hands (Abramson *et al.*, 1943; Freeman *et al.*, 1936; Gellhorn and Steck, 1938), so that at least a partial compensation occurs and the effects of anoxia are mitigated. In decompensated cardiac patients, however, no such increase in blood flow occurs, to judge from the results of the work of Landt and Benjamin (1938). If the increase in cardiac output did occur, it

would constitute an additional source of strain in patients with hearts already damaged. Moreover, it appears that the respiratory center in cardiac patients in failure is hypersensitive to oxygen lack (Landt and Benjamin, 1941, Graybiel *et al*, 1937) and therefore small changes in arterial blood oxygen saturation should aggravate dyspnea Additional evidence of the importance of the apparently mild degree of arterial anoxemia that occurs in cardiac decompensation is afforded by data on the effects of oxygen therapy. Relief of symptoms, when it occurs, is usually associated with an elevation of the level of arterial blood oxygen saturation to or toward normal (Barach and Richards, 1931; Barach and Woodwell, 1921*a*; Cohn *et al*, 1932; Richards and Barach, 1934; Schoen and Derra, 1930), venous blood oxygen content also rises (Barach and Woodwell, 1921*a*)

Pulmonary factors are for the most part responsible for lowered arterial blood oxygen saturations in patients with cardiac decompensation not associated with congenital heart disease These factors include inefficient respiration, impaired mixing in the lungs, edema of the alveolar walls and, in some instances of severe mitral stenosis, organic changes in the alveoli (page 285) Tachypnea, of whatever origin, may also lower the arterial blood oxygen saturation (Meakins, 1920, 1922; Meakins and Davies, 1920, Barach and Woodwell, 1921*b*)

The strikingly low oxygen content of the peripheral venous blood in chronic congestive failure has been known for several decades and has been observed by many authors (Harrop, 1919; Lundsgaard, 1918*a,b,c*; 27), Harrison and Pilcher (1929) found no deviation from the normal. Low jugular venous blood saturations were found by McMichael (1939), Himwich and Fazekas (1944) and Raab (1931). The lowered venous blood oxygen levels are consequent to decreased cardiac output relative to the oxygen consumption of the tissues. During exercise the inability of the cardiac output to increase in proportion to the increased needs of the body (page 8) results in a further fall in oxygen content of the venous blood; this is particularly striking in the exercising limb, where the levels may approach zero (Weiss and Ellis, 1935).

The fall in venous blood oxygen is more constantly found and more marked than in the arterial blood oxygen; consequently the arteriovenous oxygen difference is increased. The venous blood oxygen

level is a better indicator of the state of the tissues than is the arterial.

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13. *Alveolar Air and Arterial and Venous Blood Carbon Dioxide Content. Carbonic Anhydrase. Arterial and Venous Blood pH. Electrolyte Patterns*

A decrease in alveolar air carbon dioxide content or tension has been noted in patients with cardiac decompensation by many authors (Dautrebande, 1928; Peabody *et al.*, 1916, 28). This decrease parallels the increase in respiratory minute volume and thereby is related to the degree of dyspnea to some extent. Indeed, it is caused by hyperventilation out of proportion to carbon dioxide production in the body, and indicates central respiratory stimulation. As Pearce (1917, 1921) and Dautrebande (1928) pointed out, circulatory in-

sufficiency may cause it; however, central stimulation by other mechanisms, such as reflexes, anoxia, cortical influences, and the direct effect of fever on the medullary centers, may act likewise. Lowering of alveolar carbon dioxide content is not diagnostic, but it does distinguish cardiac dyspnea from that due to diffuse pulmonary disease (in the absence of fever).

Since the free carbonic acid of the arterial blood varies as the alveolar carbon dioxide tension, the former must also be diminished in cardiac decompensation. A large number of observers have recorded measurements of arterial whole blood carbon dioxide content or tension, and arterial plasma bicarbonate in patients with congestive failure; the values reported are usually low in the normal range or below it (Cobet, 1924; Fraser, 1927; 29), the degree of lowering varying with the severity of hyperventilation. The carbon dioxide content of arterial blood is above normal in only a small minority of patients with chronic cardiac decompensation; these have either diffuse primary pulmonary disease as well (Campbell *et al.*, 1923; Fraser, 1927, Fraser *et al*, 1928; Peters *et al.*, 1927*a*,*b*; Winkler and Crankshaw, 1938) or else very severe uncomplicated congestive failure with extreme degrees of pulmonary engorgement and edema (Campbell *et al*, 1923, Fraser, 1927) In either of these conditions the diffusion of carbon dioxide across the alveolar walls may be impeded.

Changes in venous whole blood carbon dioxide tension and in venous serum bicarbonate at rest are variable (Pearce, 1921, Pilcher, *et al*, 1930; Scott, 1919; 30), in most instances the values are in the normal range. When cardiac decompensation is extreme, however, the venous blood carbon dioxide content may be somewhat lowered (Scott, 1919, Peters, 1917), but not to the extent to which the arterial level is depressed McMichael (1939) found the jugular venous carbon dioxide tension elevated in dyspneic patients.

Since the pH of the blood depends on the ratio of bicarbonate to carbonic acid, it is clear that a variety of changes can occur in the blood of patients with cardiac decompensation. The arterial blood pH is within the normal range or somewhat elevated (Fraser *et al.*, 1928, 31), depending apparently on the severity of hyperventilation. In severe hyperventilation there is marked lowering of the alveolar

air carbon dioxide tension with a corresponding fall in carbonic acid content of the arterial blood. The ratio of bicarbonate to carbonic acid is increased and the arterial pH usually rises.

That more patients with severe congestive failure do not manifest this trend toward arterial alkalosis may be due to the increases in blood lactic acid frequently present (page 86). A small group of patients, consisting principally of those with additional diffuse organic pulmonary disease, show carbon dioxide retention with a consequent lowering of arterial blood pH due to this factor in itself The venous blood pH is usually normal, although in occasional instances it may lie a little above or below the normal range (Peabody, 1914, Fraser *et al*, 1922; Harris *et al.*, 1935; Peters and Barr, 1921; Pilcher *et al.*, 1930, Shiskin, 1937, Sonne and Jarlöv, 1918). However, the difference between arterial and venous blood pH is greater than normal.

It is clear that the above-described changes in arterial blood are the consequences rather than the causes of hyperventilation and dyspnea at rest Lowering of arterial carbon dioxide content and hydrogen ion concentration appears to provide a compensatory mechanism for stasis, a means is provided whereby each unit of blood passing through the tissues may take up more carbon dioxide. The discussion of Pearce in 1921 is still pertinent in this respect; of particular interest in regard to cardiac decompensation is his general conclusion that if the venous blood carbon dioxide is high relative to the alveolar, then the circulation must be inadequate. Arterial acidosis is not a cause of dyspnea in chronic congestive failure, at least at rest, but a tendency toward *tissue* acidosis, consequent to carbon dioxide retention secondary to stasis, apparently is partly responsible for the hyperventilation of cardiac decompensation, Peabody (1915) pointed out that the respiratory response to inhalation of carbon dioxide is similar in patients with congestive failure to that shown by patients with uremic acidosis

A number of authors have studied the carbon dioxide carrying power of the arterial and venous blood by measuring part or all of the dissociation curve (Fraser, 1927; Meneely and Kaltreider, 1943; 32). Although the results are usually within the normal range, in some instances the curve is somewhat low and in others, apparently normal, some rise occurs in recovery. Meakins, Dautrebande and

Fetter (1923) determined the carbon dioxide dissociation curves of both arterial and venous blood in the same decompensated patients and found normal values for the former, but a lowering of the latter. They ascribed this depression of the venous curve to loss of base to the tissues consequent to stasis (Dautrebande, Davies and Meakins, 1923). It is difficult to understand, however, how this lost base returns to the arterial blood so as to restore the curve of that blood to normal. Their findings are also difficult to interpret in the light of those of other workers who found a depression of the arterial carbon dioxide dissociation curve.

Fraser, Graham, and Hilton (1924) corroborated the observations of Meakins *et al.* (1923) on the lowering of the venous curve as compared to the arterial, but in their experience this change was not limited to patients in whom stasis existed. They pointed out that the arterial blood dissociation curve and pH were the result of the passage of *mixed* venous blood through the lungs and that comparing arterial with venous blood taken from one part of the body, usually the arm, did not permit one to draw conclusions concerning the relation between the arterial and *mixed* venous blood.

The cause of the slight lowering of the blood carbon dioxide curves that may occur in congestive failure is not established, but it is not unlikely that lactic acidosis may play a part in some instances. Not to be overlooked in this connection is the possibility that the administration of excessive amounts of ammonium chloride may also be a factor (page 193). In the presence of moderate or severe acidosis a shift in the oxygen dissociation curve to the right should occur. Lewis *et al* (1913) found this change in the venous blood in some of their patients, but Meakins *et al* (1923) could not corroborate this observation when they studied arterial blood; available data indicate that significant acidosis does not occur at rest in cardiac decompensation.

After exercise, the carbon dioxide capacity of the blood (Schmitz and Preston, 1927, Groag and Schwartz, 1927, Harris *et al.*, 1935) and the pH (Dennig and Prodger, 1933, Eppinger *et al.*, 1926; Harris *et al.*, 1935; Pilcher *et al*, 1930) usually fall abnormally in cardiac patients. This shift toward acidosis has been correlated with elevated blood lactic acid levels by Harris, Jones and Aldred (1935). Although the carbon dioxide content of arterial blood (Cullen *et al.*,

carbonate and chloride levels. The third group is a small one and includes patients in whom there is probably an element of renal insufficiency accounting for the loss of plasma base. The data of other authors (Atchley *et al.*, 1923; Gilligan *et al.*, 1934; Winkler and Crankshaw, 1938) may be grouped in the same manner. Many authors (page 195) have also observed that diuresis is often associated with a lowering of plasma chloride and an elevation of bicarbonate concentration.

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14. *Tissue Gas Tensions*

Techniques for measuring the tissue gas tensions directly are difficult, laborious and of doubtful accuracy; methods for measuring carbon dioxide tension appear to be considerably less inaccurate than those for oxygen. Only a few data obtained by these methods in patients with chronic cardiac decompensation are available. Del Baere (1939) and Meyer (1935, 1936) found abnormally low oxygen tensions and normal or high carbon dioxide tensions Sibree (1941) studied four patients and concluded that the oxygen tension was in the normal range, while the carbon dioxide tension was high Much more work will have to be done before data of this sort can be considered conclusive.

Data derived from studies of venous blood gases are pertinent. The oxygen tension of tissue fluid cannot be higher than that found in the venous blood, it may be lower, since the opening of the widely distributed arteriovenous anastomoses may arterialize the venous blood to a greater or lesser degree, so that gas concentrations in the latter may not always accurately reflect conditions in the capillaries. Accordingly, since low venous oxygen contents are the rule (page

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also Jervell (1928) found in addition a marked increase in lactic acid output in the urine of such patients. A number of authors (Bielschowsky and Thaddea, 1932; 36) found an abnormally high level of blood lactate and a prolonged curve of disappearance after the injection of lactate in decompensated cases, with a good correlation between these conditions and the degree of failure. In a general way the resting blood lactate content and the level to which it rises after exercise or injection of lactate are related to the severity of congestive failure, although numerous exceptions are to be found. Hallock (1939) found a good correlation between the blood lactate level and severity of dyspnea. However, Dennig *et al.* (1931) reported that the accumulation of 10 milliequivalents of lactate completely prevents work by precipitating early exhaustion; lesser concentrations have a corresponding effect Accordingly, excessive rises in lactate may possibly prevent the development of maximal dyspnea by limiting muscular effort.

The fact that the abnormal lactate metabolism which occurs in congestive failure resembles that seen in liver disease (Schumacher, 1928, Adler and Lange, 1927, Beckmann, 1929, Dresel and Himmelweit, 1930, Valentin, 1925) has led some authors to conclude that both originate in liver damage However, Dresel and Himmelweit (1929, 1930) observed that although the blood lactate levels, both at rest and after exercise on a staircase, might be similar in patients with cardiac and with hepatic diseases, yet the metabolism of lactate in the peripheral tissues, as studied by means of dynamometer experiments, is impaired in congestive failure but not in liver disease. It appears, therefore, that the hepatic damage of congestive failure plays only a contributory role in the lactic acidosis seen in that condition. Tissue anoxia seems to be the most important factor in this regard. Weiss and Ellis (1935) correlated the rise in blood lactate with the fall in venous blood oxygen during exercise in some patients. Inhalation of oxygen may lower elevated blood lactate in patients with cardiac decompensation (Barach, 1931; Barach and Richards, 1931, Jervell, 1928); this phenomenon may be associated with "storage" of oxygen (Jervell, 1928) Conversely, anoxia induced in normal subjects by the breathing of air containing low concentrations of oxygen may give rise to an increase in blood lactic acid content at rest (Jervell, 1928; Bock *et al*, 1932, Friedemann *et al.*, 1945) or

70), it must be concluded that tissue anoxia exists in chronic congestive failure. Similarly, the tissue carbon dioxide tensions must be at least as high as those which are found in the venous blood, that is, they are normal or high (page 77)

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15. *Blood Lactate and Pyruvate*

In 1913 Lewis *et al.* reported the finding of an increase in the blood lactic acid level in some patients with congestive failure. Clausen (1922) later noted a parallelism between blood lactic acid level and clinical condition in a patient with cardiac decompensation. Many additional observations have been recorded since that time. Some authors report levels within the normal range in their patients with myocardial insufficiency at rest (Weiss and Ellis, 1935; **33**), while others describe somewhat elevated levels in some or most of their patients (Jervell, 1928; **34**) Although a significant increase in blood lactate concentration is found infrequently in decompensated patients at rest, exercise almost always results in abnormally high levels which fall to normal slowly after the patient returns to the resting state (Meakins and Long, 1927; Jervell, 1928; **35**). Groag and Schwartz (1927) and Harris, Jones and Aldred (1935) noted a simultaneous fall in blood alkali reserve and pH. These authors and

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in the blood o
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during work (Asmussen and Chiodi, 1941; Dill *et al*, 1931; Lundin and Ström, 1947; Tepperman and Tepperman, 1948). The blood lactate curve found in normal subjects or decompensated cardiac patients after intravenous injection of lactate is lowered in both groups by the simultaneous breathing of air enriched with oxygen (Bielschowsky and Thaddea, 1932), Hewlett, Barnett, and Lewis (1926) and Asmussen and Nielsen (1946) found a lowered blood lactate level and urine excretion when normal subjects exercised while breathing air enriched with oxygen.

Although the evidence strongly favors tissue anoxia as the cause of lactic acidosis in congestive failure, it is not possible to rule out thiamin deficiency as an additional factor in some instances. Studies of pyruvate metabolism in cardiac decompensation are fragmentary. Bueding, Wortis and Stern (1942) found it normal in patients at rest, while Taylor, Weiss and Wilkins (1937) and Yanoff (1942) found the blood level elevated commonly. Goldsmith (1947, 1948) also found it elevated in patients in cardiac failure and noted that the lactate-pyruvate ratio in these cases was similar to that in instances of beriberi; the ratio returned to normal when thiamin was given Exercise in congestive failure causes an abnormally great and prolonged increase in blood pyruvate (Yanoff, 1943). The observation of Wilkins, Weiss, and Taylor (1939) that the curve of blood pyruvate after intravenous injection of that material is normal in congestive failure may be due to their use of too small a dose. Elevation of the blood pyruvate levels occurs less readily than does increase in lactate in normal subjects made anoxic (Friedemann *et al*, 1945). Elevation of the blood pyruvate level not only contributes to acidosis but also may possibly impair muscular function (page 151)

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16. *Oxygen Debt. Cost of Work*

The relation of accumulation of lactic acid in the blood during work to oxygen debt after work is well established. It is to be expected, therefore, that the oxygen debt in cardiac patients after performance of a given task would be abnormally large and prolonged; this has been shown in patients with various degrees of failure (Nylin, 1933, 1937, 1938, 1939, Eppinger *et al.*, 1925; 37). Compensated cardiac patients take up normal amounts of oxygen

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gested by the findings of Jervell (1928), Uhlenbruck (1930), Knipping *et al.* (1932) and Jansen *et al.* (1932), who found that patients with cardiac decompensation took up abnormally large amounts of oxygen when exposed to high concentrations; in some instances this effect is masked by a simultaneous decrease in oxygen consumption associated with relief of dyspnea and hyperventilation. Although this "storage" is in part consequent to the retention of oxygen in saturating the undersaturated arterial blood often found in decompensated cardiac patients, another factor may be the discharge of accumulated oxygen debt. Thus, in cardiac patients with high blood lactate levels during rest, the blood lactate falls after these patients breathe air enriched with oxygen (page 87). In addition, the fact that the process of "storage" lasts for approximately forty minutes (Uhlenbruck, 1930) in cardiac patients also suggests an effect other than the raising to normal of the level of arterial blood oxygen saturation, for the latter requires only five or ten minutes.

The high cost of work and the smallness of the maximal oxygen debts that cardiac patients are capable of developing (Harrison and Pilcher, 1930; Meakins and Long, 1927) seriously impair ability to do work in congestive failure. Factors limiting the maximal oxygen debt include muscular weakness and the early development of dyspnea The latter is at least in part related to lactic acidosis, which also has the effect of limiting work *per se*, according to Dennig *et al* (1931), the presence of 10 milliequivalents of lactate in the blood completely prevents exertion because of exhaustion

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during the performance of work (Alt *et al.*, 1930; Bowen and Carmer, 1926, Herbst, 1928*b*; Zaeper *et al.*, 1939), whereas with patients in failure the intake of oxygen during exertion is low, depending on the severity of the condition (Herbst, 1928*b*; Harrison and Pilcher, 1930; 38). Carbon dioxide output may be low also (Campbell, 1934; Campbell and Sale, 1927) The size and duration of the oxygen debt after work is to some extent consequent to the deficit in oxygen intake during work. This is related to failure of the cardiac output to increase normally during exertion in cardiac patients (page 8) and also to impaired pulmonary function It is to be noted in regard to the latter that in normal subjects the application of a suitable chest binder lowers vital capacity (Altschule *et al*, 1943, Herbst, 1928*a*; Jacobaeus *et al.*, 1935), may decrease tidal air volume (Sturgis *et al*, 1922), increases respiratory rate and minute volume at rest and in exertion (Altschule *et al.*, 1943, Herbst, 1928, Sturgis *et al.*, 1922), and also results in a decreased intake of oxygen during work (Herbst, 1928*a*) and an abnormally large debt afterwards (Jacobaeus *et al*, 1935).

Although impaired pulmonary function itself can cause all of the changes just mentioned, it is probably of secondary importance in congestive failure, oxygen intake during work is increased in primary pulmonary disease if oxygen is breathed, but this does not occur in most decompensated cardiacs (de Carrasco and Vorwerk, 1936, Herrmansen, 1938), which implies that the chief difficulty is circulatory. The importance of anoxia in relation to the size of the oxygen debt is illustrated by the observation that normal individuals breathing air containing low concentrations of oxygen have increased debts after work (Clark-Kennedy and Owen, 1926).

Another factor favoring increased oxygen debt after exercise is the increased cost of work, that is, lowered efficiency, in cardiac decompensation. The cost of work in terms of total oxygen consumption required for a given task has been found to be high (Eppinger *et al*, 1925, Harris and Lipkin, 1931; Herbst, 1928*b*, 39) except in mildly decompensated patients doing light work, where it is normal (Alt *et al*, 1930; Simonson *et al.*, 1930, Zaeper *et al.*, 1939). It is of interest that anaerobic work is inefficient in normal subjects (Asmussen, 1946).

That some patients are in oxygen debt even while at rest is sug-

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Ellis, 1933) a high degree of correlation between the presence of edema and a decrease in plasma protein level does not exist. Smirk (1936) showed that edema does not occur in noncardiac patients in whom are found plasma protein levels as low as those that occur in edematous cardiac patients.

Ellis (1933) has contributed an excellent analysis of the pathogenesis of the changes in plasma protein, from which the present discussion deviates only slightly Payne and Peters (1932), Ellis (1933) and Thomson (1934) stressed malnutrition as the principal cause of the observed diminution in plasma total protein and albumin levels, and the data of Proger and Magendantz (1936) show a fall of 50 per cent in plasma albumin in a cardiac patient in whom there was restriction of intake of food over a sixty-day period; the globulin rose in these experiments. Conversely, Ellis (1933) demonstrated the beneficial effects of a high protein intake. Several authors (Iversen and Nakazawa, 1927, Ellis, 1933, Ehrström, 1936) regard the marked albuminuria frequently seen in severe cardiac decompensation as an important contributory cause. Loss of protein as a consequence of repeated paracentesis may also be a factor (Ellis, 1933), for large amounts of protein are found in thoracic and abdominal fluids in congestive failure (page 102). The development of edema itself lowers the plasma protein level, either as a consequence of dilution of the blood or because protein is lost into edema fluids, or both Thus salt retention causes lowering of plasma protein levels (Iversen and Nakazawa, 1927, Lyons *et al*, 1944, 1945) in both normal subjects and cardiac patients That some protein does pass into tissue fluid when the venous pressure is elevated has been shown by Senator (1888) and Landis *et al.* (1932). Increased protein catabolism caused by acidosis may also be a factor in patients receiving large amounts of ammonium chloride (page 194).

Loss of edema is commonly associated with a rise in plasma protein concentration or oncotic pressure (42, Calvin *et al.*, 1940; Payne and Peters, 1932), although this finding is far from constant. Calvin, Decherd, and Herrmann (1940) and Seymour *et al.* (1942) stressed the fact that although plasma protein concentration rises, the total circulating plasma protein decreases in recovery from failure; this phenomenon suggests storage of protein.

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17. *Plasma Protein and Oncotic Pressure*

Lowering of the plasma protein level in patients with cardiac decompensation has been recognized for over a half a century (40; Payne and Peters, 1932, Ellis, 1933) On the other hand, a few authors have reported normal values for plasma protein in their patients (Moore and Stewart, 1930, Kylin, 1931, Hand, 1934). Stewart (1941) and Moore and Stewart (1930) described the plasma specific gravity as normal also, Di Palma and Kendall (1944), however, found the specific gravity low Kylin (1931), who found the plasma protein level normal, reported low values for colloid oncotic pressure, which suggests some error in his techniques It must be concluded that lowering of plasma protein level is of common occurrence in chronic cardiac decompensation

As pointed out by Payne and Peters (1932), Thomson (1934), Luetscher (1941), and Herrmann (1946), the plasma albumin is more likely to be so affected than the globulin The globulin levels are more variable and may often be elevated, according to these authors and also to Rowe (1917). As is to be expected, the plasma colloid oncotic pressure is often low (41; Smirk, 1936); marked differences between arterial and venous bloods reported by some authors (Barath and Elias, 1930; Kylin, 1931) are difficult to accept In a general way, low plasma protein levels or diminished plasma oncotic pressures are associated with the presence of edema, but in large series of patients (Cope, 1928; Payne and Peters, 1932;

GILLIGAN, D. R, M. C VOLK, and M. D. ALTSCHULE, The diffusibility of plasma calcium following parathormone administration. Comparison of the calcium, phosphate and protein concentrations of serum and edema fluids, *J. Biol Chem* **103**, 745 (1933). [40

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18. *Extracellular Fluid Volume. Edema Fluid*

Extracellular fluid volume. — Cardiac patients with edema have increased volume of fluid in the extracellular tissue spaces and in many cases in the serous cavities as well This abnormally increased volume of fluid may be enormous; the loss of fifty pounds — a third or a quarter of the body weight — during a diuresis is not uncommon in severely edematous patients Measurements of extracellular fluid volume by means of radioactive sodium (Kaltreider *et al.*, 1941), bromide ion (Brodie *et al*, 1939) or thiocyanate (Gilligan and Altschule, 1939; Molenaar and Roller, 1939; Kaltreider *et al.*, 1941; Seymour *et al.*, 1942; Fowell *et al.*, 1948) have been made in patients with heart disease; extracellular fluid volume may equal one-half to two-thirds of the body weight, as compared to the normal of a fifth or a quarter. Gilligan and Altschule (1939) found that such measurements were subject to error in the presence of marked generalized edema or single large accumulations of fluid in a body cavity, unless sufficient time were allowed for equilibration of injected thiocyanate. In addition, the colloid content of the transudate apparently influences the distribution of thiocyanate, so that the presence of transudates of relatively high protein content, such as peritoneal and pleural effusions, makes the precise measurement of extracellular fluid volume impossible

The most recent work (Kaltreider *et al*, 1941) suggests that thiocyanate combines with blood lipids These measurements are, however, accurate when such large effusions are absent. Molenaar and Roller (1939) found the extracellular fluid increased in some cardiac patients even in the absence of overt signs of failure; after recovery

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Gm. per hundred cubic centimeters After these patients lost their edema, these authors placed tourniquets at a pressure of 40 cm-of-water about their limbs and obtained fluids containing 0.4 to 0.9 Gm.; they concluded that the fact that edema fluid from sick cardiac patients contained no more protein than that obtained from such patients after recovery indicated that no increase in capillary permeability occurred in cardiac decompensation. However, tourniquets at that pressure slow the blood flow (Friedland, Hunt and Wilkins, 1941), and there is no way of estimating the direction or the amount of difference in flow in the extremities of their cardiac patients when sick without tourniquets and when "recovered" with them in place; studies of venous blood oxygen would have been helpful. Senator (1888) recorded the interesting observation that putting a tourniquet about the limb of a cardiac patient with edema may raise the protein content of the edema fluid by as much as 40 per cent More recently, Landis *et al* (1932) published data in support of this finding in normal subjects, estimating an edema fluid protein level of 0.3 at tourniquet pressures up to 60 mm-of-mercury and of 1.5 at 80 mm-of-mercury. It is not possible, therefore, to evaluate the significance of the findings of Stead and Warren (1944) or to accept their conclusions.

Pleural fluids (44, Luetscher, 1941) and ascitic fluids (45; Luetscher, 1941) in cardiac patients contain appreciably larger amounts of protein than are to be found in subcutaneous edema fluids Pleural fluids usually contain 1.0 to 3.0 Gm per hundred cubic centimeters and abdominal fluids from 1.0 to as much as 5.0 Gm The reason for these variations in protein content in fluids derived from various parts of the body is not apparent Luetscher (1941) made a systematic study of the protein in pleural and abdominal fluids and found that such fluids taken from cardiac patients contained more protein than those removed from patients with renal disease or cirrhosis of the liver. Fluids obtained from cardiac patients also contained relatively more albumin and less globulin than either the plasma of the same patients or the fluids of patients with renal disease or cirrhosis. The significance of these differences is not clear, but it is to be noted that the deviations in the ratio of albumin to globulin in transudates in congestive failure resemble those seen in toxic edema due to increased capillary permeability (Chanutin *et al.*, 1947).

from severe congestive failure with edema the volume of extracellular fluid is still increased, often by half its normal volume (Altschule, 1937, Seymour *et al*, 1942) The body may actually harbor six or seven liters of edema fluid when the patient is considered to be free of edema or is even declared to be "cured of right heart failure."

Ionic constitution of edema fluid.—That cardiac edema is an ultrafiltrate derived from plasma appears to be established (Loeb *et al*, 1922; Hastings *et al*, 1925; Gilligan *et al.*, 1934*a*,*b*; Folk *et al.*, 1948). The fact that the ionic constitutions of plasma and of edema fluid are not identical is related to the differences in colloid content and is explicable on the basis of the Donnan equilibrium; edema fluid contains significantly more chloride than plasma, and changes in other electrolyte ratios have also been found. There seems to be no need to invoke vitalistic phenomena to explain edema formation in chronic congestive failure Changing the ionic constitution of blood plasma by giving bicarbonate or ammonium chloride or by diuresis causes corresponding changes in edema fluid (Gilligan *et al.*, 1934*a*)

Protein content.—Many authors have studied the protein content of subcutaneous edema fluid by the use of a variety of methods (43, Bramkamp, 1935). The reported values obtained by acceptable methods have usually been less than 0 6 Gm. per hundred cubic centimeters, although occasional levels of 1.0 Gm per cent or more have been described Bramkamp (1935) found little or no globulin in subcutaneous edema fluid drawn from patients with chronic cardiac decompensation The fact that cardiac subcutaneous edema fluid contains more protein than the edema fluid of patients with renal disease (Beckmann, 1921; Falta and Quittner, 1917; Fodor and Fischer, 1922, Hoffman, 1889; Kerkhof, 1937; Vancura, 1931) or malnutrition (Falta and Quittner, 1917) has been recorded and suggests an increase in capillary permeability in congestive failure However, Vancura (1931) found the ratio between plasma and edema fluid protein the same in cardiac and renal disease On the other hand, Bramkamp (1935) found no relation between plasma and edema fluid protein in cardiacs. Stead and Warren (1944) obtained fluids from the subcutaneous tissues of the edematous extremities of cardiac patients and found their protein content to lie between 0.1 and 0.5

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The joints in edematous extremities of cardiac patients contain much more fluid than normal (Coggeshall *et al.*, 1941), but the mucin, protein, and total solid concentrations are all lower.

All types of edema fluids frequently show elevation of protein concentration during and after diuresis (Beckmann, 1921; Claussen, 1932; Gilligan *et al.*, 1933, 1934*a*; Iversen and Johansen, 1929); the finding of Stead and Warren (1944) that the edema fluid protein does not change under these circumstances is discordant. The occurrence of such changes makes the use of data on tissue fluid content difficult to interpret in relation to variations in capillary permeability.

A finding of unknown significance is that the cholinesterase content of edema fluid varies with that of the plasma and also with the amount of protein in the blood (Grob *et al*, 1947).

Lipid contents — The cholesterol, total lipid and fatty acid concentrations of transudates vary with the protein content of these fluids and not with the plasma concentrations of any of them (Man and Peters, 1933).

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19. *Blood Volume and Viscosity. Hemoglobin and Erythrocyte Count*

Most authors report an increased blood volume in patients with congestive failure (46, Gibson and Evans, 1937, Meneely and Kaltreider, 1943; Seymour *et al*, 1942) Plasma, red cell and total volumes are all increased to approximately the same degree except in cor pulmonale, where the plasma volume remains normal, only the red blood cell mass and total volume increasing (Richards, 1945) Bock (1921) described normal values in his one case, while others found it to be increased only inconstantly (47); these authors used methods of low accuracy. Wollheim (1931) and his followers, Goldbloom *et al* (1935, 1939), concluded that either increased or decreased blood volumes might occur in cardiac failure and evolved the theory of two forms of failure, "plus" and "minus." However, their data actually show increased values in most instances of chronic congestive failure. Moreover, the methods used by the authors whose results are discordant have been criticized by Gibson and Evans (1937) It is concluded that the plasma volume is increased in all cases of uncomplicated chronic cardiac decompensation

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decompensation is not known Judging by the reported changes in plasma protein level (page 97), some dilution of the blood plasma may occur in patients with edema consequent to heart disease, but the cause of the phenomenon is also unknown. Salt retention is a possible factor, for increasing salt intake in normal subjects or in cardiac patients dilutes the blood (Iversen and Nakazawa, 1927; Lyons *et al*, 1945*b*) and increases the blood volume (Krauel, 1941; Lyons *et al.*, 1944, 1945*a*, *b*; Warren and Stead, 1944; Grant and Reischman, 1946) However, dilution, if it occurs, would not explain the increase in circulating red cell mass which also has been noted The generalized vasodilatation, suggested by the large number of dilated capillaries visible in the skin of decompensated patients, is probably also related to the abnormally large blood volume. However, whether generalized capillary dilatation results in an increased blood volume, or vice versa, cannot be stated with certainty. Anoxia may also be responsible for the increased blood volume, much as in dwellers at high altitudes (Douglas, 1910, Hurtado, 1932, Hurtado *et al.*, 1945, Laquer, 1924; Lippman, 1926, Smith *et al.*, 1925) or patients with severe pulmonary disease (page 304) However, these persons usually exhibit a considerable increase in hematocrit and circulating red cell mass which accounts for most or all of their increased blood volumes.

It is possible also that the increased blood volume of cardiac decompensation represents in part an attempt to compensate for a low cardiac output It is obvious that if the flow of blood through a unit volume of tissue is low, anoxia will result This can, to some extent, be obviated if a larger volume of blood is kept in contact with the unit volume of tissue for a longer period of time. It is interesting in this connection that the manifestations of surgical shock may occasionally be observed to develop in patients who enter the hospital with severe congestive failure, if they are treated by means of too enthusiastic diuretic therapy.

Still another factor has been emphasized by Landis *et al* (1946) in a most convincing way These authors showed in animals that the normal decrease in plasma volume which occurs during exertion is exceeded greatly if unusually high and prolonged elevations of venous pressure occur in exercise when the heart is incompetent. An increase in blood volume, participated in both by plasma and by

After recovery from congestive failure, following digitalis or other forms of therapy, a decrease in blood volume occurs according to most authors (48; Gibson and Evans, 1937, Meneely and Kaltreider, 1943; Seymour *et al*, 1942), while others (49) report variable changes The latter results were, however, obtained by the use of inaccurate methods. Gibson and Evans (1937) studied a large group of patients and found a high degree of correlation between the severity of the signs and symptoms of congestive failure and the increase in blood volume. In recovery from congestive failure, the blood volume decreases toward but only rarely attains normal values. Gibson and Evans (1937), Brandt (1931), Perera (1945) and Wollheim (1931) found a parallelism between changes in blood volume and venous pressure in individual cases; the increased blood volume was not responsible, however, for more than a small part of the venous pressure rise, since diuresis caused marked decreases in blood volume and only small changes in venous pressure. In addition, Meneely and Kaltreider (1943) failed to find this parallelism in all stages of failure.

The question whether or not exercise in cardiac decompensation might force blood from the circulation into the hypothetical blood depots, or the other way, has been studied by a number of authors (Ewig and Hinsberg, 1931, Kaltreider and Meneely, 1940; Levin, 1935; Wollheim, 1931). The best work in this regard is that of Kaltreider and Meneely (1940), who found a slight decrease in blood volume in decompensated patients during exercise, much as in normal subjects, in contradiction to the results of Ewig and Hinsberg (1931). Changes in blood volume in various positions have been studied by a number of authors in normal subjects. Normal individuals show hemoconcentration and decreased plasma volume after standing still for some minutes (Asmussen *et al*, 1940; Youmans *et al.*, 1934, Waterfield, 1931, Thompson *et al.*, 1928). Changes in cardiac patients have not been studied adequately; the data of de Flora and Ciravegna (1931) are not satisfactory Nevertheless, it is almost certain that still-standing, or lying in an inclined position with feet down, probably causes a small decrease in blood volume, of unknown duration, in patients with congestive failure.

The reason for the increases in blood volume in chronic cardiac

known that venous blood is more fragile than arterial (Creed, 1938; Whitby and Hynes, 1935) and in cardiac decompensation the blood is more venous than normal in one respect, namely, its oxygen content. Exposure to high oxygen tensions in vitro decreases erythrocyte fragility (Butler, 1912; Creed, 1938; Dacie and Vaughan, 1938), and Booth (1941) demonstrated in dogs that the breathing of air low in oxygen content increased erythrocyte fragility. However, Whitby and Hynes (1935) concluded that the increased fragility of normal venous blood was related to its increased carbon dioxide content. Other observers showed that locally induced stasis in animals (Ham and Castle, 1940, Tsai *et al.*, 1940) or in man (Waller, 1939) resulted in an increase in erythrocyte fragility; oxygen lack or carbon dioxide excess appear to have been ruled out, however, as causes of this phenomenon (Waller, 1939; Tsai *et al.*, 1940). The observation of Francescon (1936) that cells which show increased resistance to hemolysis in dilute salt solution are also present in the blood in congestive failure is of interest in relation to the reported occurrence of target cells in this disorder (Valentine and Neel, 1944).

Changes in blood viscosity might be expected to occur when the number of red blood cells per cubic millimeter is increased. Bence (1905) thought that retention of carbon dioxide caused the changes in viscosity but showed that inhalation of oxygen by cyanotic patients lowered the viscosity of the blood. Extensive studies on the blood viscosity in congestive failure have been made by Albers (1937), Markson (1936) and Rogen (1940). The results of Albers (1937) are probably inaccurate, for he described an increase in viscosity but also found the plasma protein level elevated in congestive failure. The data of Markson (1936) and of Rogen (1940) are not presented in sufficient detail for analysis, but it appears that both observed normal or low values in edematous patients, while patients with marked cyanosis, especially with severe pulmonary disease and polycythemia, usually showed increased viscosity of the blood. Oxygen in such instances might very well reduce the viscosity, as Bence (1905) found.

Altana and Pulino (1947) have discussed the blood leucocytes in congestive failure.

erythrocytes, is a compensatory change that protects the body against the effects of a fall in blood volume to very low levels.

The increase in cardiac residual blood claimed by Nylin is discussed elsewhere (page 20).

The red blood cell count and hemoglobin percentage show no consistent change in cardiac decompensation, in most instances normal values are observed. The individual cell size is also within the normal range (Price-Jones, 1921). Patients in severe congestive failure with marked cyanosis, especially those with severe pulmonary disease (Richards, 1945), may show an elevation of the red blood cell count and hemoglobin percentage However, as pointed out above, the total circulating red cell mass is always increased in cardiac decompensation, even in the absence of abnormally high erythrocyte counts and hemoglobin levels. During recovery a transitory rise in hematocrit may be noted (50; Gibson and Evans, 1937) since the plasma volume decreases more rapidly than the red cell volume.

Ott (1939) examined the sternal marrow in patients with congestive failure and found hyperplasia of the red cell forming elements, with a return to normal after recovery. Ehrstrom (1936) and Waller *et al* (1940) studied the changes in the blood during the various stages of congestive failure and found reticulocytosis with decompensation, and the expected evidences of blood destruction during recovery. The latter consisted in the finding of increased urobilinogen excretion in the stool, an observation recorded by others as well (Adler and Sachs, 1923, Francescon, 1936; Weiss, 1930). Eppinger and Walzel (1926) found an increase in bile pigment in the duodenum. The increase in urine urobilinogen discussed elsewhere (page 129) may also be due in part to increased blood destruction However, Localio *et al.* (1941) and Watson (1937) found no increase in bile pigment excretion such as might indicate blood destruction, their patients may have been studied when in a steady state.

The fragility of the erythrocytes to hypotonic saline solution is increased in cyanotic or decompensated cardiac patients (Francescon, 1936; Greenthal and O'Donnell, 1921; Waller *et al*, 1940), but why this increased tendency toward hemolysis does not become markedly active until recovery begins is not clear. The cause of the increased fragility is likewise not established, although it is well

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20. *Renal Function*

Striking changes in renal physiology are of frequent occurrence in congestive failure, although at postmortem examination not much more than congestion and edema of the kidney are to be found.

The renal blood flow, first measured by means of inulin clearance, is decreased in congestive failure (Seymour *et al*, 1944, Mokotoff, Ross and Leiter, 1948; Fowell *et al.*, 1948); similar findings have recently been noted in measurements of arteriovenous oxygen difference estimated from samples of blood obtained by catheterization of the renal vein via the antecubital vein (Warren *et al.*, 1944; Merrill, 1946). The renal blood flow is decreased to a far greater extent than the cardiac output in patients with congestive failure (Merrill, 1946); apparently vasoconstriction must also occur. The vasoconstriction is not relaxed by spinal anesthesia (Mokotoff and Ross, 1948). It is, therefore, not surprising that low values for urea clearance have been found in patients with congestive failure (Porge, 1939, Seymour *et al.*, 1944), these values return to or toward normal with improvement, as shown by these authors and also by Stewart and McIntosh (1928). The decreases in urea clearance noted are not in themselves sufficiently marked to cause nitrogen retention, but they must play a contributory role. Filtration is decreased but reabsorption is in normal proportion (Merrill, 1946, Mokotoff, Ross and Leiter, 1948). The filtration fraction is increased (Mokotoff, Ross and Leiter, 1948). During exercise in patients with compensated heart disease filtration may fall to a level found to be consistent with salt retention (Merrill and Cargill, 1947, 1948).

The nitrogen retention that occurs in severe congestive failure is well known. In addition to the above-noted lowered urea clearance, other causative factors must exist. One such factor is oliguria itself. Renal stasis, caused by venous obstruction, was shown by Rowntree, Fitz and Geraghty (1913) and by Winton (1931) to cause a decrease

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(Burch and Reaser, 1947, Mokotoff and Ross, 1947); it can be produced in dogs by partially ligating the renal veins, even though the obstruction may not be severe enough to cause oliguria (Rowntree, Fitz and Geraghty, 1913). This is discussed more fully elsewhere (page 123).

Another consequence of renal stasis is a reduction in phenolsulfonphthalein excretion. This occurs in patients with congestive failure (Agnew, 1914; Frothingham and Smillie, 1914, Rowntree *et al.*, 1912, 1913, 1915) and can be induced in dogs by obstructing the renal veins (Rowntree, Fitz and Geraghty, 1913).

Albuminuria is almost a constant finding in moderate or severe cardiac failure Nearly three-quarters of a century ago a number of authors, including Posner (1880), showed that albuminuria could be produced by obstructing renal blood flow. Posner (1880) and Telemann (1910) were among the early workers who showed that such albuminuria was caused by the escape of albumin into the glomerular capsules. Less complete stasis, such as that caused by constricting the renal vein so as to raise the venous pressure, has also been shown to cause albuminuria (Rowntree, Fitz and Geraghty, 1913, Winton, 1931) Clinically, however, albuminuria occurs in many decompensated cardiac patients in whom the venous pressure is within normal limits, the blood flow may be greatly decreased in such instances (Merrill, 1946) The albuminuria of congestive failure is usually of moderate degree, although at times it may approach in quantity that observed in renal disease. Brummer (1946) claimed that proteinuria increased with effort in cardiac patients but not in normal subjects, his conclusion is not supported with regularity by his data or by what is known of the physiology of exercise

Stewart and Moore (1930) investigated the formed elements in the urine in congestive failure and observed a rough parallelism between the number of casts and leucocytes and the clinical condition in a group of patients; erythrocytes tended to persist in abnormal numbers even after recovery from severe cardiac failure. Rowntree, Fitz, and Geraghty (1913) in their experiments on obstruction of the renal vein in animals showed that the number of formed elements in the urine corresponded fairly well with the degree of renal congestion.

in the volume of urine formed. Whether or not tissue anoxia secondary to stasis is the effective cause of the oliguria has not been established A similar oliguria has been described in animals breathing air containing low volumes of oxygen (Van Liere *et al*, 1935; Toth, 1937; Schnedorf and Orr, 1941); in rats, however, polyuria was the response to anoxia (Silvette, 1943). It is difficult to evaluate the importance of these studies of the effects of anoxic anoxia, since marked blood chemical changes also occur. The formation in chronic congestive failure of antidiuretic substances, which has been demonstrated in acute nephritis and eclampsia, and which would act to cause oliguria, has not been established, but the possibility must be considered. It is to be noted in this connection that the urine in uncomplicated congestive failure before treatment has a high specific gravity, as observed many years ago by Rowntree and Fitz (1913).

Whatever the cause of the reduced urine volume in cardiac decompensation, it must, when marked, lead to nitrogen retention. Chesley (1937, 1938*a*, *b*) has shown that in normal individuals the urine is maximally concentrated with regard to total solids, urea, total nitrogen and creatinine when the volume reaches levels as low as 500 to 750 cc per day, decreases in volume below that range result in no further increase in concentration. The importance of oliguria in the genesis of nitrogen retention is demonstrated by the effects of mercurial diuresis. The injection of mercurial diuretics causes no increase in renal blood flow (page 198), but does greatly increase urine volume, the diuresis usually results in the return to normal of previously elevated blood nonprotein nitrogen levels. The nitrogen retention in congestive failure may occasionally give rise to levels of 60 to 80 mg. per hundred cubic centimeters of nonprotein nitrogen in the blood; blood creatinine levels may also be elevated occasionally (Popper *et al.*, 1937; Gavrila *et al*, 1929; Messina, 1936). It is important to note that these findings must not be considered contraindications to the use of mercurial diuretics, the elevated blood nonprotein nitrogen levels of uncomplicated cardiac decompensation are only infrequently severe and are always transitory, disappearing with treatment.

Retention of salt occurs in congestive failure (page 122) and this probably related to renal congestion, for it has been correlated with reduction in renal blood flow and reduced sodium clearance in man

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patients; Warren and Stead (1944) also demonstrated an increase in plasma volume, and hemodilution is also known to occur (Iversen and Nakazawa, 1927). However, Proger *et al.* (1942) also showed that the increase in respiratory minute volume and oxygen consumption, the elevation of venous and arterial pressures, the slowing of the circulation time and the reduction in vital capacity that result are prevented if the patient is digitalized. Moreover, the work of Warren and Stead (1944) is to be criticized because in the patients studied by these authors the regular injection of diuretics was stopped at the same time as the giving of large amounts of sodium chloride was begun.

The reason for the abnormal retention of salt is not clear. One explanation for the salt retention is that "prerenal deviation" of water leads to salt retention also, that is, salt is retained because edema fluid is being formed However, many authors have shown that the volume of water taken by the patient does not influence the accumulation of fluid (Barker, 1932, Proger *et al.*, 1942; Schroeder, 1941; Wolf *et al*, 1947; Leevy *et al.*, 1946) This is sometimes seen very strikingly in the case of edematous cardiac patients given urea; they exhibit a marked diuresis in spite of increased intake, occasionally reaching ten liters a day, occasioned by the severe thirst that the ingestion of large amounts of urea may cause Moreover, the fact that changing the renal function, by the injection of a mercurial diuretic, for instance, leads to the excretion of the retained sodium chloride, suggests that the kidney is at fault More than thirty years ago, Rowntree, Fitz and Geraghty (1913) induced partial renal stasis by means of ties on the renal veins in dogs and demonstrated retention of sodium chloride and also sodium iodide. It seems reasonable to conclude that stasis so changes renal function as to impair the excretion of the sodium Available evidence indicates that a reduction in renal blood flow is the rule in patients with congestive failure (page 117). Renal clearance of sodium is low (Burch and Reaser, 1947; Mokotoff, Ross and Leiter, 1948, Farnsworth, 1948; Fowell *et al*, 1948); filtration is diminished but reabsorption is in normal proportion (Merrill, 1946; Mokotoff, Ross and Leiter, 1948). Additional evidence of derangement of the function of the kidneys is afforded by the observation that when the plasma chloride levels fall in cardiac patients, the excretion of chloride ion continues (Winkler

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21. *Sodium Chloride and Water Metabolism*

Clinicians have long believed that edema formation parallels salt intake in patients with congestive heart failure. Even normal individuals gain weight when given excessive amounts of sodium chloride (Krauel, 1941; Lyons, Jacobson and Avery, 1944); they lose weight when salt intake is restricted (Krauel, 1941). These changes in weight are consequent to corresponding changes in the volume of extracellular fluid (Grant and Reichsman, 1946), although the plasma volume shows smaller parallel variations (Krauel, 1941; Lyons *et al.*, 1944, 1945, Warren and Stead, 1944; Grant and Reichsman, 1946). Increased salt intake apparently causes hemodilution also (Lyons *et al*, 1944, 1945; Warren and Stead, 1944). The venous pressure may rise slightly (Lyons *et al*, 1945; Warren and Stead, 1944, Grant and Reichsman, 1946) but the cardiac output does not change, according to Lyons *et al.* (1945).

Achard and Loeper (1901) and Rowntree and Fitz (1913) many years ago showed that edematous cardiac patients retain salt, and McLean (1915) also recognized the fact that the excretion of salt in such patients might be low relative to their blood levels. Recent studies by Futcher and Schroeder (1942) by Burch and Reaser (1947) by Threefoot *et al.* (1947), and by Burch *et al.* (1947), have confirmed these observations. Burch *et al.* (1947) have shown that the diffusion of sodium across the capillary walls is more rapid than normal in edema, the overall turnover in plasma being more rapid also while that in the greatly increased volume of interstitial fluid is slower. Schroeder (1941), Proger *et al.* (1942), Schemm (1942, 1944), Warren and Stead (1944) and Wolf *et al.* (1947) have shown how an increased salt intake alone gives rise to edema formation in cardiac

salt depletion and low plasma chloride concentrations inhibit the action of diuretics, and administration of sodium chloride enhances their action (page 197), it may at times be preferable to avoid unduly severe dietary salt restriction. The difficulties involved in preparing the low salt diet recommended by some authors, the extremely unpalatable character of the food it offers to anorectic cardiac patients, the facts that the low salt diet is also low in animal protein, that cardiac patients on a low salt regimen excrete less salt than is normal under the circumstances, that many of the effects of salt intake are obviated by digitalization (Proger *et al*, 1942) and that too rigid restriction of sodium chloride intake inhibits the action of diuretics, all suggest that the avoidance of such severe restriction of salt intake over extended periods of time might be wise

As has been pointed out above, severe restriction of water may be harmful. There is no evidence, however, that forcing of fluids is beneficial in congestive failure (Wolf *et al.*, 1947), in this condition the diuretic action of water is lost, for reasons which are not established (Fremont-Smith *et al*, 1930; Crutchfield *et al*, 1948) and indeed excessive intake of fluid may possibly depress sodium excretion in congestive failure.

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and Crankshaw, 1938; *Futcher and Schroeder, 1942) even though* the blood level is one which in normal persons would be accompanied by the cessation of all urinary chloride output. The exact mechanism responsible for these derangements of renal function is not clear.

An additional factor making for later salt retention is an initially low salt intake. It has been demonstrated that subjects maintained on a low salt intake retain sodium chloride when given it later in larger amounts (Rowntree and Fitz, 1913; Loeb *et al.*, 1932, McCance, 1936; White and Findley, 1939). As salt restriction is prolonged, the body retains what is given it with increasing tenacity. In extreme instances, oliguria, fall in urea clearance and glomerular filtration, and nitrogen retention may occur (Landis *et al.*, 1935; Wilkinson and McCance, 1940; Mokotoff, Ross and Leiter, 1948; Hellman *et al.*, 1948) It is probable that this extreme stage does not often occur in congestive failure, for it has been shown (Reaser and Burch, 1946) that cardiac patients on a restricted intake of salt lose an abnormally small amount of it. Parrish (1949) has shown an increased excretion of urinary corticoids in edema and this may have some bearing on the retention of salt also.

The antidiuretic substances that have been shown to exist in the nephritic and eclamptic urine have not been demonstrated in the urine of cardiac patients. The administration of large amounts of *salt in normal rats (Gilman and Goodman, 1937) or in man* (Hickey and Hare, 1944) has, however, been shown to result in the release of an antidiuretic substance within the body. Since cardiac patients do not excrete salt as rapidly as normal subjects it is reasonable to assume that this antidiuretic mechanism is activated in edematous cardiac patients at a lower level of salt intake than in normal individuals. It is perhaps pertinent also that liver inactivates antidiuretic hormones normally (Heller and Urban, 1935); in the presence of liver damage this function might possibly be impaired. In addition, several studies have demonstrated that dehydration also results in the release of an antidiuretic substance in several species of animal (Pickford, 1945) and it is, therefore, possible that excessive reduction of water intake, such as is still practiced by some physicians in treating cardiac patients, may act in a similar fashion.

Rigid restriction of salt intake may result in a lowering of plasma *chloride* and base levels (Loeb *et al.*, 1932; McCance, 1936). Since

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The abnormal porphyrinuria that may occur in congestive failure (Thiel and Kammerer, 1933, Dobriner, 1936, Dobriner and Rhoads, 1940; Kaunitz, 1938) is probably also a manifestation of impaired liver function, its occurrence is not universally reported in congestive failure, however (Localio *et al*, 1941).

Disturbances of urobilinogen excretion have also been noted Increased urobilinogen content in the urine is described either as such (53; Chavez *et al.*, 1943*a*,*b*; Waller *et al*, 1940) or by implication in the form of an elevated urine to stool ratio (Adler and Sachs, 1923, Localio *et al*, 1941). Robertson *et al* (1932) found it normal, however Although this phenomenon may be influenced by the abnormal blood destruction observed in some stages of congestive failure (page 110), the chief cause must be hepatic dysfunction.

Meakins (1927) found that jaundice, when it occurred, was most marked over the upper chest and face. He also stated that bile pigment is not found in edema fluids, although his data show otherwise. Andrews (1924) detected appreciable amounts of bilirubin in ascitic fluid taken from a cardiac patient and Altschule and Volk (1937)

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22. *Hepatic Function. Porphyrinuria*

Hepatic enlargement is one of the commonest and often one of the earliest signs of cardiac decompensation Although exertional dyspnea usually precedes enlargement of the liver, the latter may be noted weeks or months before edema or râles can be detected. This phenomenon is readily understandable in the light of Brunton's (1908) observations on the enormous distensibility of the liver. In very severe failure jaundice may become manifest, with bile in the urine, but this is not the rule. In spite of the absence of frank jaundice, however, some increase in the serum bilirubin level is common in cardiac decompensation (**51**; Jolliffe, 1930; Chavez *et al.*, 1943); the ratio of direct-reacting to indirect-reacting bilirubin is normal (Cantarow *et al*, 1942) In general the degree of elevation of the plasma bilirubin corresponds with the severity of the cardiac failure, but values much above 2.0 mg. are not common. The degree of bilirubinemia is not necessarily related to the increase in size of the liver.

Although the prothrombin time is normal (Cotlove and Vorzimer, 1946), other tests of liver function usually are not. Dye retention may occur (**52**; Bernstein *et al.*, 1942), although Epstein *et al.* (1927) found none, and Piersol and Rothman (1928) found it only infrequently and in mild degree in patients in failure. Dye retention is related to slow hepatic blood flow, according to Ingelfinger (1947).

in certain stages of failure, and increased fragility of the red blood cells has also been reported in patients with cardiac decompensation (page 110). It is of interest that the breakdown of hemoglobin causes greater elevation of blood bilirubin level in patients with cardiac decompensation than in normal subjects (Gilligan, Altschule and Katersky, 1941). Ernstene (1932) pointed out that the jaundice of heart disease is due to a combination of increased production and diminished excretion of bile pigment.

The diminished liver function in heart failure is in itself rarely severe enough to be clinically important. It is of significance because it indicates the presence of liver damage which may lead to cirrhosis. That so few patients with congestive failure develop clinically important cirrhosis of the liver is unquestionably due to the fact that few of them live long enough (Katzin, Waller and Blumgart, 1939). Many authors have reproduced in animals the central scarring which is said to be typical of cardiac cirrhosis, but Bolton (1914) observed portal infiltration and fibrosis The latter observation is significant in view of the fact that not infrequently patients in whom a clinical diagnosis of "cardiac" or central cirrhosis of the liver is made, are found, on autopsy, to show unmistakable evidences of portal cirrhosis (Altschule, 1938; Katzin *et al*, 1939).

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also found it in this as well as other edema fluids in cardiac patients with normal or elevated serum bilirubin levels. The quantity of bilirubin present in edema fluids roughly parallels but is always less than that found in the serum at the time; the protein content of the edema fluid also appears to influence to some degree the bilirubin content (Altschule and Volk, 1937).

The abnormal liver function observed in cardiac decompensation is reflected in the typical histologic changes found in the liver, but the extent of the two is not always parallel Many authors have related the degree of hepatic engorgement and central necrosis to the increased venous pressure of cardiac decompensation. Mallory (1911), however, pointed out that if back pressure were the cause of necrosis, it should involve the entire liver lobule, since the increased pressure must be distributed everywhere. Indeed, the pressure must actually be higher in the periphery of the liver lobule if the gradient of pressure necessary for flow of blood is to be maintained Mallory felt that a toxin of some sort was responsible

Diminution in hepatic blood flow, with the development of abnormal venous blood unsaturation, occurs in congestive failure (Myers and Hickam, 1948). It is probable that anoxia is the important factor in the genesis of the altered histology and physiology of the liver in cardiac decompensation Neubauer (1913) and Mattson (1929) showed that anoxia causes a striking increase in the size of the liver in animals; the opposite findings of Griffith and Emery (1930) are discordant. Rich (1930) found the typical histological changes of congestive failure in the livers of patients with anoxemia due to severe anemia and in animals exposed to low oxygen tensions. McMichael (1937) found central necrosis in the livers of cats when the inflow of blood into the liver was diminished Resnik and Keefer (1926), Barron (1931) and Rich (1930) observed a low liver function as measured by the bilirubin excretion test in anoxic animals. The outflow of bile from the liver has also been shown to be depressed by anoxia in animals (Schnedorf and Orr, 1941); men at high altitudes often show elevation of plasma bilirubin (Hurtado *et al*, 1945).

On the other hand, available evidence indicates that the hyperbilirubinemia of cardiac decompensation is not due solely to faulty excretion of bile pigment, for several observers (page 110) have found increased amounts of bile pigment in the stool or urine, or both,

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changed (Machlachlan and Thacker, 1945) except when anoxia is extreme.

More direct experimental evidence bearing on gastro-intestinal function is afforded by studies of the effects of stasis induced by ties placed about the portal vein. The rise in gastro-intestinal venous pressure so induced slows absorption (McMichael and Smirk, 1933; Wells, 1940; Stickney, *et al.*, 1947) and results in a type of gastritis (Gulzow and Afendulis, 1938). In addition, edema of the stomach and intestines has been shown to delay emptying (Barden *et al.*, 1938; Mecray, *et al*, 1937).

Any of the physiologic changes just mentioned could explain the gastro-intestinal symptoms associated with cardiac decompensation and thereby throw some light on the mechanism of malnutrition which commonly develops in cardiac patients.

The distention that occurs in severe congestive failure can be quite severe. Distention of the small intestine in itself results in a derangement of the circulation whereby blood is shunted through arteriovenous anastomoses and away from the capillaries (Lawson and Ambrose, 1942, Oppenheimer and Mann, 1943), thereby further depressing absorption and possibly digestion also

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23. *Gastro-intestinal Function*

Anorexia, nausea, distention, gaseous eructations, constipation and flatulence are frequent complaints in moderate or severe congestive failure. Data on gastro-intestinal function in patients with chronic congestive failure, are, however, fragmentary. Costadoni (1938) and Levitan and Alexeief-Berkman (1935) found greatly lowered gastric acid values, even after histamine The latter also found retarded gastric emptying. Costadoni (1938) found an abnormal amount of nitrogen in the stool, while Levitan and Alexeief-Berkman (1935) reported partly digested food. This finding was regarded by these authors as evidence of hypermotility of the intestines, but this cannot be related definitely to congestive failure, since three-quarters of their patients had worms or protozoa in their stools. Further studies clearly are necessary.

Studies of the effects of anoxia on gastro-intestinal function are pertinent, but are difficult to evaluate since the conditions under which they were performed gave rise to the loss of considerable amounts of carbon dioxide from the blood; this loss causes a depression of secretion of gastric acidity (Delhougne, 1927; Browne and Vineberg, 1932, Delrue, 1934). The consequences of experimental anoxia are also difficult to relate to the tissue anoxia of congestive failure, because in the former the arterial blood oxygen saturation falls far below that commonly encountered in congestive failure, but this change is compensated for by an increase in cardiac output (page 70), so that the state of the tissues cannot be determined from the data reported. At any rate, the effects of experimentally induced anoxia on gastro-intestinal motility have been reviewed by Van Liere (1942) and include depressed gastric motility, lessened force of gastric contractions, decreased gastric tone, slowed gastric emptying time associated with pyloric spasm, no change in small intestinal motility and slowed colonic function. Anoxia does not influence intestinal secretion, but does lower the volume of gastric secretion and secretion of acid and chloride (Van Liere, 1942). Van Liere further showed that absorption from the small intestine is also affected by anoxia, that of saline solution and of glycine being depressed, while that of glucose and of water is increased; absorption of fat is un-

administration of a test dose by mouth. A study by Pollack *et al.* (1940) in patients with congestive failure gave similar results after the injection of thiamine intramuscularly, but the methods used by these authors are not specific and the period during which they collected urine may have been too short. The fact that diuresis may remove thiamine from the body has been reported (Williams and Bissell, 1944). The statement of Goldsmith (1948) that abnormal lactate-pyruvate ratios, indicative of thiamine deficiency, occur often in congestive failure is difficult to evaluate. Also pertinent is the finding of Grieg and Govier (1943), who showed that simple anoxia disturbs the utilization of thiamine and leads to a depletion of tissue cocarboxylase (thiamine diphosphate). It is apparent that the nutrition of cardiac patients has not been studied adequately

The fact that decompensated cardiac patients develop low plasma protein levels and lose their normal tissue tension because of loss of flesh is obviously of importance in the genesis of edema Thiamine depletion, which probably occurs in almost all patients with congestive failure of some duration, must not be overlooked as a factor making for increased severity of the signs and symptoms. Occasionally patients are seen in whom the usual therapeutic measures for cardiac decompensation are partly or entirely without benefit and who, because of overt clinical evidence of vitamin B deficiency, are given vitamin B complex parenterally, after which a remarkable improvement in the symptoms of cardiac decompensation occurs.

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24. *Nutrition*

Nutritional studies on congestive failure are few in number. The previously discussed fall in plasma protein level (page 96) has been ascribed in part to malnutrition, but data that show a negative nitrogen balance are scanty (Payne and Peters, 1932). These authors also referred to the finding of a marked positive balance during recovery from failure, but extensive data were not presented. It must be borne in mind that the elaboration or resorption of large amounts of edema fluid containing appreciable amounts of nitrogen make such studies difficult Harrison (1945) has shown that the measured intake of protein and also of vitamins often is low in sick cardiac patients Robinson, Melnick, and Field (1940) also found the ingestion of thiamine to be low in decompensated cardiacs. These authors showed in addition that the urinary excretion of thiamine is low after the

is also decreased (Altschule, 1943; Knipping *et al.*, 1932; Peabody and Wentworth, 1917; McClure and Peabody, 1917; Rubow, 1908). A few studies in cardiac patients show that the relief of abdominal distention which follows paracentesis for ascites relieves dyspnea, lowers the oxygen consumption and diminishes the respiratory minute volume (Resnik *et al.*, 1935*a*, *b*). In dogs, excessive distention may ultimately cause respiratory failure (Coombs, 1922).

The rise in intra-abdominal pressure which distention may cause is reflected by the corresponding rise in femoral or iliac venous pressures noted in human subjects or in dogs (54; Burwell, 1938). This increased pressure in the veins of the leg must aggravate the tendency toward edema If distention is severe enough to elevate intrapleural pressure, an increase in venous pressure is also found in the tributaries of the superior cava (Brams *et al*, 1933; Burwell, 1938; Ferris and Wilkins, 1937, Frey, 1923, Griffith *et al*, 1934), abdominal paracentesis may result in a fall in the venous pressure (Burwell, 1938; Ferris and Wilkins, 1937, Griffith *et al*, 1934, Olmer, 1938). It is apparent, therefore, that a considerable degree of impairment of venous return from the extremities may develop consequent to the increased intra-abdominal and intrathoracic pressures resulting from distention (Emerson, 1911) A similar disturbance in flow through the abdominal viscera is suggested by the observation of Bradley and Bradley (1944) that the inferior caval pressure is high in man and the renal blood flow decreased when the intra-abdominal pressure is elevated. Although the impairment of venous return consequent to the distention that may develop in congestive failure may not result in a fall in cardiac output (Bielschowsky, 1932; Resnik *et al*, 1935*b*) or increase in circulation time (Wall, 1939) at rest, it probably prevents or limits the rise in output of the heart which should occur during exercise, thereby contributing to dyspnea and weakness, and favoring an abnormally increased oxygen debt

Additional consequences of increased intra-abdominal pressure are oliguria and albuminuria (Bradley and Bradley, 1944, Thorington and Schmidt, 1923) the results apparently of decreased renal blood flow, hepatic blood flow is also diminished (Bradley, 1946).

It is clear from the foregoing discussion that the symptoms of congestive failure may be greatly reduced when intestinal distention is relieved or ascites removed. Patients with edema may occasionally

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25. *Abdominal Distention*

The distention that results from accumulation of very large amounts of ascites or of intra-intestinal gas in patients with cardiac decompensation gives rise to changes in circulation and respiration which aggravate the symptoms of congestive failure.

Studies of the lung volume and its subdivisions are fragmentary but in good agreement. Distention of the abdomen decreases the residual air volume only slightly and, although the functional residual air is appreciably diminished (Altschule, 1943; Bittorf and Forschbach, 1910), it is doubtful whether this lessening of the space available for respiration is in itself harmful. The reserve air, however, decreases almost to zero (Altschule, 1943; Bittorf and Forschbach, 1910, Knipping *et al.*, 1932; Rubow, 1908), which indicates that the intrapleural pressure is much more positive than normal and approaches atmospheric pressure (Prinzmetal and Kountz, 1935). The latter change has actually been measured in the dog (Frey, 1923). Loss of the normal negative intrapleural pressure impairs respiratory efficiency. The complemental air volume is also greatly diminished (Altschule, 1943; Bittorf and Forschbach, 1910; Knipping *et al*, 1932), indicating a corresponding degree of decrease in the expansibility of the lungs This loss of normal ability of the lungs to expand may give rise to a compensatory increase in respiratory minute volume relative to oxygen consumption at rest (Knipping *et al*, 1932) with aggravation of dyspnea, there is an abnormally large oxygen debt after exercise (Nylin, 1937, 1938). Since the reserve and complemental air volumes are much smaller than normal, the vital capacity

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exhibit a spontaneous diuresis or may become responsive to mercurial diuretics after abdominal paracentesis. The manifestations of impaired respiration and circulation appear to vary with the intra-abdominal pressure rather than with the changes in the volume of the abdomen and its contents; the loss of extensibility of the abdominal wall which occurs with distention (Sodeman and Burch, 1937) is therefore important.

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26. *Basal Metabolic Rate. Blood Iodine*

Elevation of the basal metabolic rate in congestive failure has been noted by many authors (55, Peabody *et. al.*, 1916, 1917, 1922). Peabody, Wentworth and Barker (1917) and Resnik and Friedman (1935) found a close correlation between the degree of dyspnea and the rise in metabolism; the latter authors also correlated the rise in metabolic rate with the ratio of respiratory minute volume to vital capacity. Resnik and Friedman (1935) felt that the increased muscular effort associated with dyspnea was the cause of the change in metabolism. However, the slight rise in rectal temperature found in severely decompensated patients (page 29) may also be a factor. Both elevation of rectal temperature and severe dyspnea occur in the most severely decompensated patients, and the increased metabolism could well be related to both at the same time.

The apparent degree of elevation of the basal metabolic rate found in some instances may be misleading because the values obtained may be too high. This is owing largely to the fact that it is frequently impossible for the anxious or sick cardiac patient to assume a truly basal state. Another factor leading to error in measuring basal metabolism in severely decompensated patients is the fact that such patients, when exposed to the high concentration of oxygen in the ordinary type of basal metabolism apparatus, take up excessive amounts of oxygen (page 93) in saturating their abnormally unsaturated arterial blood or in discharging their oxygen debts

Blood iodine. — The common finding of elevated basal metabolic rates in patients with congestive failure has stimulated interest in the blood iodine level in such cases. Most authors agree that the blood iodine level is normal in patients in failure, including those with elevated metabolic rates not due to thyrotoxicosis (Kisch, 1934; Lohr, 1936; Turner *et al.*, 1940). The findings of Veil and Sturm (1925), who reported elevated levels in patients in failure with rapid heart rates, and a fall in blood iodine to or toward normal after the administration of digitalis, are discordant.

the fact that most patients in failure hyperventilate and should, therefore, vaporize more than a normal amount of water in the lungs (Christie and Loomis, 1932; Burch, 1946*a*); loss via the skin is low (Burch, 1946*b*). Impairment of cutaneous blood flow is probably responsible for this phenomenon Di Macco (1921), who measured water loss directly, reported low values only over edematous skin, but his methods are of doubtful accuracy

The attempts of Conti (1932), Neurath (1939), and Zak *et al* (1929, 1935*a*, *b*) to establish the theory that the body colloids of edematous patients actually absorb water from the air, since the measured insensible perspiration is negative, have been widely criticized on the ground of errors in technique (56, Newburgh and Johnston, 1942).

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27. *Insensible Perspiration*

The insensible water loss is normal or, at times, abnormally low in congestive failure (**56**; Kesterman and Schleining, 1936) in spite of

of tourniquets in normal subjects led him to rule out increased venous pressure as the cause of the lymphatic stasis observed by him in cardiac decompensation, anoxia may be the factor responsible. It is probable, however, that the elevated venous pressure found in many patients with congestive failure is also a factor preventing normal lymphatic function, for increases in venous pressure must be transmitted to the lymphatic vessels.

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29. *Central Nervous System Function*

Patients with moderate or severe congestive failure not infrequently show evidence of psychic disturbances ranging from inability to concentrate or mild changes in personality to coma or psychosis.

Gross (1940) studied intellectual function by means of a number of tests of intelligence and attempted to correlate changes so revealed with variations in circulation time in cardiac patients. Although cerebral function improved with amelioration of cardiac decompensation, the changes were usually not parallel to those in circulation time.

Neither gross motor change, such as paralysis or impairment of reflexes, nor measurable impairment of sensation occur However, studies made by Simonson and Enzer (1941) and Enzer *et al* (1942) on the fusion frequency of flicker, a measure of the maximal frequency of motor impulses, do show impairment of that function in congestive failure. It is of interest that similar changes occur in anoxia also (Enzer *et al.*, 1942). It is not unlikely that the limited ability to do physical work commonly seen in congestive failure is related in part to this phenomenon.

The circulation through the central nervous system has not been studied extensively in congestive failure Calhoun *et al.* (1931)

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28. *Lymphatics*

The studies of McMaster (1937) on the lymphatics of the skin in patients with congestive failure are important in relation to the mechanism of formation of cardiac edema. McMaster found dilatation and valvular incompetence of the lymphatic channels and complete absence of lymph flow in the skin of edematous legs of patients Administration of diuretics caused no apparent change in the function of the lymphatic vessels. Elevating the edematous limb, however, caused small increases in lymphatic flow. McMaster's inability to reproduce the typical lymphatic stasis of congestive failure by means

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30. *Skeletal Muscle Function*

It is well known that many patients with cardiac decompensation complain of generalized muscular weakness. Indeed, in some instances this complaint is a much more prominent symptom than dyspnea. Under the latter circumstances an interesting parallel may be drawn with the effects of exercise under anoxic conditions at high altitudes, as described by Edwards (1936), exhaustion occurred before the subjects could work long enough to develop a significant rise in blood lactate.

The muscular weakness of cardiac decompensation may be related to abnormal creatine metabolism, for Kindler (1936) studied the incidence of creatinuria in patients with cardiac decompensation and found it present in all patients with signs of severe failure, Herrmann (1935), without recording data, also described creatinuria as common in cardiac decompensation Kindler (1936) reported regression of creatinuria with improvement and believed that the observed deviation from the normal creatine metabolism was a result of the effect of anoxia on skeletal muscle. However, the phenomenon may possibly be one manifestation of a generalized metabolic disturbance due to severe illness; malnutrition and prolonged rest in bed probably play contributory roles Other mechanisms which possibly may be involved in giving rise to muscular weakness and easy fatigability are disturbances in the enzyme systems that participate in muscular action. Data in this regard are lacking but studies have been made on the synthesis of acetylcholine which are of interest Anoxia has been shown to retard the synthesis of acetylcholine in vitro (Quastel *et al.*, 1936; Mann *et al.*, 1938; Welsch and Hyde, 1944); Torda and Wolff (1945) found the synthesis of acetylcholine to be depressed by blood drawn from an arm exercised under conditions of ischemia The observations of Nachmansohn and John (1944), who found depression in the synthesis of that substance in the presence of elevated pyruvate in concentrations that may be reached in man, may be related Put-

studied the jugular venous blood and found no evidence of slow flow, while McMichael (1939) and Himwich and Fazekas (1944) found the cerebral arteriovenous oxygen difference to be increased as a rule. The latter authors concluded that the very low jugular venous oxygen content found in their patient accounted for the patient's cerebral symptoms. White *et al.* (1942) studied the effect of anoxia on the brain in dogs and concluded that lack of oxygen caused cerebral edema. In addition, elevation of spinal fluid pressure occurs in cardiac decompensation as a result of elevation of the venous pressure (page 49). All these mechanisms are probably responsible for the central nervous system symptoms found in patients with chronic cardiac decompensation

The occurrence of Cheyne-Stokes respiration is probably also a consequence of impaired cerebral function in congestive failure. In animals, periodic breathing has been induced either by elevation of the cerebrospinal fluid pressure or by slowing of the blood flow through the brain (Greeley and Greeley, 1930).

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31. *Tissue Pressure. Cutaneous Pressure and Distensibility*

A number of authors (Krogh *et al.*, 1932; Landis and Gibbon, 1933; Youmans *et al*, 1934) have in the past stressed the importance of changes in tissue pressure in edematous patients and their role in limiting the formation of edema. Burch and Sodeman (1937) and Sodeman and Burch (1937) measured the subcutaneous tissue pressure in edematous cardiac patients and found it greatly elevated, but never above the venous pressure, diuresis after the injection of salyrgan lowered it to or almost to normal In general the tissue pressure varied with the amount of edema, but in the chronic state the relationship was not present, since the tissues had lost much of their elasticity (Sodeman and Burch, 1938); distensibility decreased as edema fluid increased and tissue pressure rose. As is to be expected, the intracutaneous pressure also is elevated in the presence of edema (McMaster, 1946), earlier work purporting to show the opposite (Hajen, 1927; Holland and Meyer, 1932) is inaccurate, according to McMaster (1946) All authors agree that as edema forms the increase in tissue pressure exerts more and more of an inhibiting effect on transudation, with stretching of the skin to the point of loss of distensibility playing a similar role In the chronic state, however, this limiting effect is lessened, apparently because of repeated stretchings and also as a consequence of loss of flesh due to malnutrition.

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nam and Merritt (1941) earlier recorded the fact that pyruvate depresses muscular action. The rise in blood pyruvate that occurs in cardiac decompensation is discussed elsewhere (page 88).

Harrison *et al* (1930) described lowering of the potassium content of skeletal muscle in congestive failure. These authors regarded this finding as indicative of impairment of buffering power; it is possible that it has a more specific significance in muscle function.

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Smirk therefore concluded that capillary permeability is increased in chronic cardiac decompensation.

On the other hand, McMichael and Morris (1936) and Henry *et al.* (1946) reported plethysmographic studies of short duration from which they concluded that induced anoxia does not increase capillary permeability in normal man. These authors presented no data, so that analysis of their findings is impossible Moreover, anoxia in such experiments may induce vasoconstriction (Henry *et al.*, 1947*a*) and so reduce filtering area, and increase in rate of blood flow may counteract to some extent the lowering of arterial oxygen saturation When conditions of low venous oxygen saturation are induced, an increase in capillary permeability occurs (Henry *et al*, 1947*b*).

Stead and Warren (1944) studied the edema-fluid protein in cardiac patients and compared it with the protein content obtained in normal subjects after the application of tourniquets, they found no increase in the former over the latter and, therefore, concluded that no increase in capillary permeability occurred in congestive failure. Stead and Warren (1944) further found that the application of tourniquets to the limbs of normal subjects and of cardiac patients resulted in elaboration of fluid of similar protein content in both groups. The validity of this comparison is not established and, in addition, many authors have shown (page 102) that cardiac subcutaneous edema fluid has a higher protein content than that obtained from patients with renal disease or cirrhosis

Stead and Warren also presented data on two patients with arterial anoxemia consequent to chronic pulmonary disease and found that subcutaneous fluid that developed in these subjects after application of a tourniquet was not different in protein content from the normal These authors presented no measurements of venous blood oxygen content, data which are important since the response to anoxia in patients with normal hearts is an increase in velocity and volume of blood flow (page 70); the tissues in the patients studied may have been less anoxic than the arterial blood oxygen level indicated. Indeed, there is no conclusive evidence that it is valid to use the protein content of a fluid as a measure of permeability.

In this connection it should be remembered that the protein content of edema fluid often rises during diuresis in cardiac patients and also that in the same patient pleural and ascitic fluids usually have

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32. *Edema*

Tissue anoxia — The role of anoxia in the genesis of cardiac edema has been discussed for many years, but available data bearing on this matter are incomplete and in part discrepant. Careful work (Barach and Richards, 1931, Richards and Barach, 1934) *has shown* that some edematous cardiac patients respond to the administration of air enriched with oxygen by a profuse diuresis, only to regain their edema when removed from the oxygen tent. Anoxia was evidently of primary importance in these patients, for the administration of oxygen caused *no change in cardiac output and the disappearance of* edema was followed, rather than preceded, by a lowering of the venous pressure. Anoxia may well account also for the loss of abnormally large amounts of fluid from the blood to the tissues found by Dautrebande *et al.* (1923) after occlusion of the arterial flow in a limb. Smirk's (1936) *experiments* demonstrated a tendency in edematous cardiac patients [illegible] ounts of tissue fluid at [illegible] means of *plethysmo-* [illegible] ire to the same level above the measured plasma oncotic pressure in normal subjects and in patients with cardiac decompensation resulted in the elaboration of larger amounts of this fluid in the latter than in the former.

supplanted by the precise quantitative studies of Krogh *et al.* (1932) and of Landis *et al.* (1932, 1933), and the relationship is now established. Similar studies on the elaboration of tissue fluid in the lungs have been made by Warren and Drinker (1942). It is clear that extreme rises in venous pressure, to 30 or 40 cm-of-water, may by themselves cause the appearance of edema in the tissues. However, the relation of these findings to the moderate increases in venous pressure commonly observed in congestive failure is not established. Certainly the contention of Reichsman and Grant (1946), that the role of elevated venous pressure is paramount in the formation of edema, is much too far-reaching a conclusion to be derived from their observation that venous pressure rises before weight is gained when digitalis is omitted in congestive failure. Clinically, it has long been known that some patients with venous engorgement do not have edema and that, conversely, some patients with cardiac edema do not have venous engorgement. Measurements of venous pressure in heart disease (page 34) show much overlapping of values in edematous and nonedematous cardiac patients A large series of patients, excluding those with thyroid diseases, nephritis, emphysema, pericarditis and tricuspid disease, has been analyzed from this point of view (Altschule, 1938). Eighty-three with no history or evidence of congestive failure had venous pressures ranging as high as 11.8 cm-of-water; of these only three had levels of 11 cm-of-water or more. Of thirty-three with congestive failure, but no history or evidence of edema, seven had venous pressure levels above 11.0 and ranging as high as 14.5 cm-of-water. Thirty-five patients admitted to the hospital with edema, but who became free of visible edema and remained so at rest in bed, had venous pressures ranging as high as 14.0 cm-of-water, in eleven the pressure was above 11.0 cm-of-water. Of fifteen patients who regained edema constantly although at rest in bed, eight had venous pressures above 11.0 and as high as 18 2 cm-of-water, while seven had pressures between 0 8 and 7.1 cm-of-water These observations on the lack of correlation between increased venous pressure and edema formation in congestive failure have been corroborated by studies in congestive failure by other authors (Winsor and Burch, 1946; Merrill, 1946), in tricuspid disease (Altschule *et al.*, 1937, 1940) and in patients with superior vena caval obstruction (Smirk, 1936; Altschule *et al*, 1945).

protein contents many times that of the subcutaneous fluid (page 103). The situation becomes further confused when it is realized that even normal capillaries are believed to be freely permeable to water and salt, any increase in permeability must, therefore, refer to protein. However, variable amounts of protein do pass through the capillaries normally and if a small additional amount passed through, it would probably draw water with it and so make its presence undetectable. It is apparent that even if normal subjects and edematous cardiac patients have approximately equal tissue fluid protein contents, large amounts of protein must have entered the tissue spaces in the cardiac patients to maintain that protein concentration in the edema fluid. The fact that studies by means of dyes show no increase in capillary permeability in congestive failure (Lange, 1944) is not helpful, for studies with dyes are notoriously misleading in this respect

If anoxia results in increased elaboration of fluid in cardiac patients, it may act by giving rise to vasodilatation which would *exaggerate* whatever tendency toward increased filtration existed as a consequence of other factors, Krogh (1929) and Landis (1928) showed that anoxia causes capillary dilatation That this phenomenon accounts for part or all of the effect of anoxia in cardiac patients in whom other mechanisms for edema formation are already operative cannot be ruled out on the basis of available data, and it is clear that further studies are indicated. On the other hand, the fact that simple anoxia, induced by breathing air depleted of oxygen, has been demonstrated to cause increased water content (White *et al.*, 1942) or a profuse flow of lymph from several organs (Gesell, 1928; Maurer, 1940; Warren and Drinker, 1942; Warren *et al*, 1942) strongly suggests that the effect of anoxia may be specific increase in capillary permeability. The work of Landis (1928), of Saslow (1938) and of Pappenheimer and Soto-Rivera (1948), which showed that extreme degrees of anoxia cause increased permeability of the capillaries, may or may not be applicable to the more moderate degrees of tissue anoxia which exist in cardiac decompensation.

Increased venous pressure. — Elevation of filtering pressure is an important factor favoring the elaboration of increased amounts of tissue fluid. The approximate observations of Mende (1919), Drury and Jones (1927) and McMichael and Morris (1936) on the relation of filtering pressure to edema formation in the extremities have been

Diminished tissue pressure. — The elaboration of tissue fluid depends not only on intravascular conditions favoring transudation, but also on extravascular factors which resist the escape of fluid into the tissues Landis and his co-workers (Krogh *et al.*, 1932; Landis *et al.*, 1932, 1933) have studied this relationship in normal man, and Sodeman and Burch (page 153) have made clinical studies bearing on it in patients with congestive failure. The ease with which edema develops in cachectic patients with lax subcutaneous tissues exemplifies the importance of lowered tissue pressure in accelerating the formation of edema. Loss of flesh consequent to malnutrition is recognized as frequently present in chronic congestive failure. Prolonged bed rest results in laxity of the muscles, which probably causes similar changes It has been demonstrated (page 153) that repeated bouts of edema followed by loss of edema as a result of diuresis results in a more or less permanent impairment of tissue elasticity. Additional pertinent evidence is the fact that patients who have had repeated bouts of cardiac decompensation harbor several times as much invisible edema fluid as do those recovered from their first attack of congestive failure (page 102).

The foregoing considerations point to the conclusion that low tissue tension and loss of tissue elasticity contribute to the ease with which edema develops in cardiac patients

Sodium chloride retention — Clinicians have long been aware of the relation of sodium chloride intake to the formation of edema in congestive failure, recent physiologic studies have emphasized the importance of abnormal sodium chloride retention in this regard and also suggest that the latter is associated with impaired renal blood flow (page 122) In some cases the intake of relatively small amounts of sodium chloride seems to play a decisive role in the occurrence of edema, in most other instances it plays an important part also A discussion of the problem by Peters (1948) is of interest

Capillary dilatation. — The widespread capillary dilatation found in decompensated cardiac patients increases the filtering surface area and enhances whatever tendency toward edema formation exists as a consequence of the action of other factors

Alkalosis — Alkalosis clinically is often associated with edema formation but it is extremely unlikely that the slight degree of alkalosis of the arterial blood that may occur in markedly dyspneic pa-

It is therefore concluded that while extreme rises in venous pressure, to levels of 30 or 40 cm-of-water, may by themselves cause the appearance of edema, the moderate increases in venous pressure commonly found in congestive failure merely constitute an important contributory factor, but do not result in edema formation unless additional influences are operating at the same time. The rise in venous *pressure seen in cardiac decompensation is itself the* consequence of a number of factors The occurrence of edema mostly in dependent parts is probably related to venous pressure levels but this does not explain the development of pleural effusion. It should also be borne in mind that venous pressures in the legs are higher while the patient stands still than when he is walking (Runge, 1924; Smirk, 1936, Beecher, 1937) *On the other hand, straining* raises the femoral venous pressure (page 36), as would be expected from the observed changes in intra-abdominal pressure (Keith, 1923).

Low plasma protein level. — A pronounced lowering of the plasma protein level, namely, to less than 5.0 Gm /100 cc., with a corresponding or greater fall in plasma albumin concentration, may result in the appearance of edema, as in malnutrition or the nephrotic syndrome Such marked lowering of the total protein and albumin levels is, however, rarely encountered in uncomplicated congestive failure and lesser decreases are common; the plasma total protein content usually lies between 5.5 and 6 5 Gm /100 cc. Decreases of this magnitude are, however, of importance in the genesis of edema when combined with abnormalities in other factors, since the rate of filtrations from the capillaries at a given pressure varies inversely as the plasma protein level (Krogh *et al*, 1932).

Abnormal lymphatic function. — Clinical and experimental observations have conclusively proved the occurrence of edema following injury to lymphatics It remained for McMaster (page 148) to demonstrate the absence of normal lymphatic flow in patients with cardiac edema in contrast to the striking lymphatic hyperactivity which he observed in patients with nephritic edema The mechanisms underlying the change found in chronic cardiac decompensation are obscure; it is possible that both a rise in venous pressure and anoxia may be implicated. Whatever the causes of this phenomenon, however, it is apparent that this factor is of great importance in the genesis of cardiac edema.

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tients is important in the genesis of cardiac edema, particularly since the venous blood (and presumably, therefore, the tissues also) usually shows no such change in the direction of alkalinity.

Blood histamine — Because the injection of histamine is known to cause edema, the possible role of that substance in edema formation in cardiac patients was studied by Barsoum and Smirk (1936). Although an increase in blood histamine was demonstrated in chronic cardiac decompensation by these authors, the fact that the increase is limited to the erythrocytes and not the plasma appears to rule it out as a factor in the elaboration of excessive amounts of tissue fluid in heart disease.

Conclusions. — A general conclusion based on all the foregoing considerations is that the edema of congestive failure is usually not due to the operation of any one factor. It is impossible to correlate with absolute agreement the presence of edema with changes in any one of the factors discussed. Extreme changes in a single factor, such as the venous pressure or plasma protein level, may in themselves result in the appearance of edema, but such extreme changes occur only uncommonly in uncomplicated congestive failure It appears that the formation of cardiac edema in most patients is the result of the combination of submaximal or even minimal changes in many factors. The relative importance of each of the above-discussed factors unquestionably varies from patient to patient.

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33. *Cyanosis*

Some degree of cyanosis is commonly observed in chronic cardiac decompensation. Its onset frequently precedes that of edema and orthopnea, but only uncommonly that of dyspnea, except in the cases of some patients with congenital heart disease Cyanosis may also appear relatively early in patients with marked prominence of the veins due to tricuspid valvular disease or concretio cordis. Its earliest manifestations consist of slight blueness in areas where the skin is thinnest, such as the nailbeds and the lips When generalized, it is usually most marked over the extremities of the body, namely, fingers, toes, nose, earlobes and lips.

Lundsgaard and Van Slyke (1923) have defined the conditions under which cyanosis may occur The factors of greatest importance in uncomplicated congestive failure are (i) abnormal deoxygenation of the blood present in the skin and (ii) the abnormal amount of blood in the skin It has been demonstrated by these authors that the presence of unsaturated hemoglobin in a concentration of at least 5 Gm/100 cc. of blood is necessary for the occurrence of cyanosis They also pointed out that the low blood hemoglobin concentration of severe anemia may prevent the appearance of cyanosis, conversely, the presence of polycythemia facilitates the development of cyanosis.

A high concentration of reduced hemoglobin can result from (i) lowering of the oxygen saturation before the blood reaches the tissues or (ii) extraction of abnormally large amounts of oxygen from the blood in the tissues.

Decreased arterial blood oxygen saturation — Decreased arterial blood oxygen saturation consequent to inadequate aeration of the blood in the lungs is frequently found in congestive failure (page 70) Its importance in the genesis of cyanosis is shown by the lessening of cyanosis that follows the administration of air enriched with oxygen, accompanying this improvement is a return to or to-

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34. *Dyspnea*

In discussing dyspnea it is well to bear in mind certain general considerations as to the nature of this symptom. It cannot be emphasized too often that dyspnea is a sensation and as such is not amenable to objective measurement. There is, however, a general correlation between the symptom dyspnea and the sign hyperpnea, and the latter can be measured. On the other hand, marked differences in the degree of dyspnea which are consequent to changes in subjective sensitivity can occur in different patients in whom all physiological measurements are the same, or even at times in the same patient with relative constancy of the physical status. These facts necessarily make it difficult to evaluate accurately the significance of the physiological and chemical changes that lead to dyspnea. It must be borne in mind also that hyperpnea is a response to certain abnormalities in the physiologic or chemical status of the patient and that hyperpnea itself may cause compensatory changes in the opposite direction, so that deviations from the normal, observed, for instance, in the blood, may be negligible. In addition, hyperpnea may occur as a consequence of immeasurably small changes in the blood.

For the purposes of this discussion no attempt will be made to distinguish dyspnea at rest from dyspnea on exertion The assumption will be made that similar factors are responsible for both, with the reservation, however, that the various mechanisms may be relatively more or less important in each type of dyspnea

Tissue anoxia. — Much has been written in recent years regarding the greater responsiveness to anoxia of the peripheral chemoreceptors than of the medullary centers This material is difficult to evaluate for a number of reasons. The precise localization and role of the centers that influence respiration is far from established, although the impulses that actually give rise to changes in respiratory rate and volume must obviously arise in the medullary centers. The latter may be influenced directly by changes in the composition of the blood, or by nervous impulses arising elsewhere. The sources of the latter impulses have not been completely studied. Although most of the work reported has involved the carotid and aortic bodies, there

ward normal of the arterial blood oxygen saturation. In patients with chronic cardiac decompensation, however, relief of cyanosis resulting from oxygen therapy is frequently only partial; in addition the degree of cyanosis cannot be correlated exactly with the arterial oxygen saturation.

Increased deoxygenation of capillary blood. — Calculations of capillary unsaturation demonstrate that abnormally great deoxygenation of the capillary blood occurs in congestive failure as a result of a lowered cardiac output and consequent slowing of the peripheral blood flow (Meneely and Kaltreider, 1943). Studies on the venous blood show that concentrations of reduced hemoglobin well above 5 Gm./100 cc. of blood may occur (page 71), with the resultant appearance of cyanosis.

Capillary and venous dilatation. — The widespread capillary dilitation and increased prominence of the subpapillary venous plexus exhibited by patients with chronic cardiac decompensation exaggerate the degree of blueness present. Indeed, Goldschmidt and Light (1925) have shown that these phenomena when induced in normal individuals may in themselves cause cyanosis, even in the absence of abnormal blood gas values.

It is evident, therefore, that the cyanosis of congestive failure is due to a combination of factors All factors operate in greater or lesser degrees in different patients, although the relative importance of each factor varies from patient to patient.

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clusions from experiments that represent a real masterpiece of technical proficiency.

These remarks are pertinent, for even the experiments by Bouckaert, Heymans and Samaan (1938), designed to show the primacy of the peripheral receptors in the respiratory response to anoxia, show that this response may occur when these receptors are denervated. It is not the purpose of this discussion to prove that the role of the peripheral receptors is negligible, or to derogate the work of Heymans and his co-workers who established its importance, the intent here is merely to indicate the invalidity of ascribing no role at all to the cranial centers The experiments of Gemmill *et al.* (1934), Decharneux (1934), Gesell (1939), Moyer and Beecher (1942) and Davenport *et al.* (1943, 1947), performed largely on unanesthetized or only lightly anesthetized animals, suggest that denervation of all the known pathways from peripheral receptors does not eliminate hyperpnea consequent to anoxia; the medullary centers apparently are still important in this respect Accordingly, because of all this uncertainty, it has been decided for the purposes of the present review to use the concept of anoxemia of the respiratory centers as including both the medullary centers and the peripheral receptors.

The role of anoxia in the causation of dyspnea has for many years been considered an important one There is no need to review here the large amount of experimental work done in animals and normal man on which this conclusion is based Even in normal man exercising at sea level the dyspnea and hyperventilation of exertion are considerably abated by breathing oxygen (Briggs, 1920, Hewlett *et al.*, 1926, Asmussen and Nielsen, 1946; Nielsen and Hansen, 1937). It is, however, necessary to review the data bearing on the role of anoxia in the genesis of cardiac dyspnea because of attempts which have been made to negate their importance.

That anoxia of the tissues exists in congestive failure is shown by a large number of observations These include evidence that the venous blood oxygen tension is low and that, therefore, the tissue oxygen tension must also be low The few available measurements of tissue oxygen tension support this view. More specifically, the observations of McMichael (1939) show a low concentration of oxygen in the jugular blood and a high jugular arteriovenous differ-

is evidence that other similar structures lie along the course of the pulmonary artery (Schmidt and Comroe, 1940). If all such bodies respond to changes in oxygen tension in the blood, it is apparent that the range of change for those bathed in arterial blood must be different from that which stimulates those bathed in venous blood. Thus the fact that significant arterial anoxia may be absent in many patients with congestive failure does not rule out stimulation of the respiratory center by means of impulses originating in bodies which may possibly lie along the pulmonary arterial tree, for blood traversing this portion of the circulatory system is almost uniformly abnormally deoxygenated in patients with cardiac decompensation.

Another difficulty regarding evaluation of the role of the peripheral chemoreceptors in man is that published conclusions are based on experiments done not on man but on another species, usually the dog, under anesthesia, which ordinarily depresses the sensitivity of medullary centers, thereby enhancing the relative importance of the peripheral receptors. These experiments on dogs involve extremely complicated and shocking preparations. Some of these difficulties have been emphasized by Schmidt and Comroe (1940) as follows:

Furthermore, as the reviewers know from personal experience, there is a psychological hazard in experiments like this which can easily lead to exaggeration of the value of an unusually favorable result, in the following manner. the preparation involves extensive dissection, ligation of vessels, artificial circulation, and numerous other factors, all operating in the direction of diminished effectiveness of the reflexes The experimenter must be prepared to find that a certain proportion of such preparations will have inactive reflexes, and thus he will (quite properly) ascribe to artifacts In another (and larger) group, reflexes will be present, though of variable activity and in a third (perhaps quite small) group, they will be extremely active. It is natural to regard the most striking results as those to be expected in the absence of artifacts and to publish them as the closest approach to the normal state Actually, however, the investigator can never know that to be the case; perhaps he was dealing with responses that are wholly exceptional, and, for all that he can tell, the less impressive results may really be closer to those to be expected in the average animal. Furthermore, as the experimenter's experience and skill increase, he incorporates in his technique various items and procedures which he has found helpful to bring out the desired result in maximum intensity; in so doing, he may remove the experimental conditions further and further

of anoxia in patients with this disorder is expressed largely as an increase in respiratory rate (Graybiel *et al.*, 1937).

The many factors that act to cause tissue anoxia in chronic cardiac decompensation may be divided into two groups: (i) those that cause decreased delivery of blood to the tissues and (ii) those that result from pulmonary congestion. The latter act to cause a lowering of the arterial oxygen saturation by edema of the alveolar walls and by impairment of the bellows function of the lungs Impairment of the mechanics of respiration is in turn an expression of various subsidiary factors (page 60). Shallow respiration consequent to increased pulmonary rigidity, together with poor mixing due to increased rigidity, impaired elasticity and inefficient respiration, lead to lessened arterialization of blood in the lungs It appears reasonable to believe that the increased respiratory activity of congestive failure compensates to some extent for the effects of anoxia which otherwise might be more severe However, this increased respiratory activity itself gives rise to dyspnea Inability to increase the tidal air because of pulmonary rigidity may give rise to extreme tachypnea, which by itself may result in a lowering of arterial blood oxygen saturation The high level of respiratory activity at rest, and the fact that increased pulmonary rigidity prevents normal increases in exertion, together limit respiratory reserve markedly.

Lactic acid metabolism. One of the manifestations of tissue anoxia in cardiac patients is the occurrence of increased amounts of lactic acid in the blood at rest and, more consistently and markedly, after exertion The accumulation of lactic acid in the blood, and presumably in tissues also, indicates a breakdown in the normal mechanisms involved in the oxidation of that substance. It is known that the brain itself produces lactic acid (McGinty, 1929), and there is evidence to indicate that interference with the normal rapid oxidative destruction of lactic acid produced in the respiratory center may be a fundamental cause of hyperpnea and dyspnea Gesell (1925, 1928*a*, *b*) has elaborated this concept. In addition, the lactic acid formed in muscles that are exercised under anoxic conditions acts as a strong respiratory stimulant (Barman *et al.*, 1942, 1943). Even in normal subjects, lowering of blood lactate levels during exertion by means of inhalation of oxygen results in lessened hyperventilation (Hewlett *et al*, 1926; Asmussen and Nielsen, 1946).

ence in most patients with cardiac dyspnea. A low jugular oxygen content was also found by Raab (1931) in his dyspneic cardiacs. It is pertinent to point out that slowing the cerebral circulation in animals leads to hyperpnea (Schmidt, 1928; Greeley and Greeley, 1930). Additional evidence is offered by the many observations proving the presence of increased blood lactate and pyruvate levels at rest, and more constantly and strikingly after exertion; similar significance is also to be attached to the impaired lactate tolerance and abnormally prolonged oxygen debt after exercise in patients with congestive failure. The fact that some decompensated patients store oxygen when exposed to air containing high concentrations of that gas is also pertinent. Finally, in some patients at least, a lowered arterial blood oxygen saturation points to tissue anoxia, particularly since cardiac patients do not exhibit the increase in circulation which is a normal compensatory mechanism for anoxic anoxia (Landt and Benjamin, 1938), indeed, decompensated cardiac patients are abnormally sensitive to oxygen lack (Graybiel *et al.*, 1937; Landt and Benjamin, 1941). That degrees of anoxia such as commonly exist in patients with cardiac decompensation are of importance in the causation of dyspnea is shown by the response of such patients to the administration of air enriched with oxygen, in most instances there is an immediate and striking improvement in dyspnea. Clinical improvement under such circumstances is not consequent to an increase in cardiac output or a fall in venous pressure. The changes that occur in the venous blood oxygen tension after a variety of therapeutic measures are confirmatory evidence in that return toward normal of the venous blood oxygen tension is usually associated with improvement in dyspnea.

The objection has been raised that the hyperpnea of congestive failure could not be anoxic in origin, since anoxia in normal subjects or animals is not usually associated with shallow and very rapid respiration such as occurs in congestive failure. This objection is not valid for two reasons: (i) experimental anoxia is of short duration, and there are indications that more chronic anoxia, even in normal man, may give rise to rapid shallow breathing; (ii) the increased rigidity of the lungs in congestive failure prevents a normal increase in tidal air volume, so that the increased respiratory activity

least hyperpnea, consequent to the stimulation of pressor receptors in the auricle or great vein, has been raised by Harrison *et al.* (1932*a*, *b*) and by Megibow *et al.* (1943). There is no conclusive evidence that the experiments described by these authors ruled out slowing of cerebral circulation when the right auricle or the great veins were distended. Moreover, in normal man, infusion intravenously of large amounts of fluid, so rapidly as to distend the veins and raise the venous pressure to levels found in congestive failure, does not cause dyspnea or hyperpnea (Altschule *et al*, 1938, 1942). It is not demonstrated that reflexes from this part of the circulatory system are implicated in the dyspnea and hyperpnea of cardiac decompensation.

Reflexes from other proprioceptors — The question whether other proprioceptors, located in or near skeletal muscle, may be involved in the hyperventilation of exercise in normal conditions is still a matter of dispute (von Euler and Liljestrand, 1946). The contention of Harrison *et al* (1932*a*) that these mechanisms are important in the genesis of cardiac dyspnea has little to support it.

Tissue carbon dioxide. — Direct measurements of tissue carbon dioxide tension, though scanty, suggest that elevated levels occur (page 85) Although, in general, the venous blood carbon dioxide content is within normal limits in congestive failure, McMichael (1939) pointed out that many dyspneic cardiac patients have elevated jugular venous blood carbon dioxide tensions A number of authors (page 76) have suggested that the low arterial blood carbon dioxide content and tension of cardiac decompensation constitute a compensatory mechanism to prevent accumulation of carbon dioxide in the tissues, particularly the brain, consequent to decreased flow Lowering of arterial carbon dioxide content and tension is a consequence of hyperventilation, which thereby masks the tendency toward accumulation of carbon dioxide in the tissues It is possible, therefore, that this tendency is a cause of hyperventilation and dyspnea in congestive failure

Impaired heat dispersal — A cause of cardiac dyspnea that is usually overlooked is alteration of the heat-dispersal mechanisms due to a decreased blood flow through the skin. Observations on the occurrence of low skin temperatures in spite of high rectal temperatures in cardiac decompensation strongly indicate the existence of this

That lactic acid in the blood is a stronger respiratory stimulant than mineral acids is well known; a recent discussion of this matter by Rosenbaum (1942) emphasizes this difference and points out that lactic acid has a stronger action because it is rapidly diffusible across the cell membrane.

Changes in the lungs — The increased pulmonary rigidity which decompensated patients show may by itself cause or aggravate dyspnea. The impaired expansibility which is consequent to increased rigidity makes inhalation more arduous, and the associated loss of pulmonary elasticity makes expiration more difficult. These effects cause dyspnea both in themselves and by giving rise to shallow and rapid respiration, which is inefficient. The impaired pulmonary expansibility becomes especially troublesome during exertion, where the normal response is a considerable increase in tidal air volume. The maximal possible respiration per minute is low in patients with cardiac decompensation and the elevated resting respiratory minute volume that results from inefficient respiration further encroaches on the respiratory reserve available for use during exertion.

Abnormal stimuli from the lungs — It has been shown in experiments on animals that hyperpnea results from the activation of reflexes originating in the lungs Intrapulmonary factors giving rise to stimuli that may activate these reflexes appear to be (i) abnormal rigidity of the lungs, which activates the Hering-Breuer reflex, and (ii) distention of pulmonary vessels, which activates the Churchill-Cope reflex (page 67). The nervous pathways involved in these reflexes are present in all individuals; in cardiac decompensation changes occur within the lungs, resulting in the transmission of afferent impulses to the brain which evoke a motor response, namely, hyperpnea Perception by the patient of this increased respiratory activity may result in a sensation of dyspnea There is no evidence to indicate that the congestive changes in the lungs result in dyspnea by giving rise to afferent impulses directly to the sensorium. Although reflex mechanisms have been demonstrated to be important in the manifestations of cardiac asthma (page 222), there are no data bearing on their significance in the dyspnea of chronic congestive failure.

Reflexes from the great veins. — The question of dyspnea, or at

a convincing manner changes in a given physiological measurement with the degree of dyspnea is due not only to the fact that dyspnea is a sensation and, therefore, unmeasurable, but also to the fact that the importance of each factor in the production of dyspnea varies from patient to patient.

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Chapter I — Section 34

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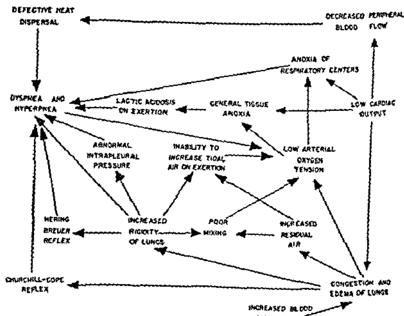
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factor (page 29). The hyperpnea that is a response to inability to disperse normal amounts of heat via the skin in cardiac decompensation (page 29) must contribute to dyspnea The fact that many patients with severe decompensation claim to experience relief of dyspnea as a result of removing bed clothes and being placed in front of an open window is in harmony with this concept (Burch, 1946).

Increased blood volume. — The increase in blood volume that occurs in congestive failure results in an increase in the amount of blood in the lungs, thereby exaggerating the pulmonary congestion which is consequent to other factors. Diuresis, which decreases the blood volume and raises vital capacity (page 196), frequently results in a striking improvement in dyspnea. The possibility that at least part of the improvement following diuresis is due to dissipation of edema of the alveolar walls is also to be borne in mind.

Conclusions. — It is apparent that cardiac dyspnea, like the previously discussed cyanosis and edema, is a consequence of the operation of a multiplicity of factors. Figure 1 indicates how these factors are interrelated The inability of various investigators to correlate in



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35. *Orthopnea*

Orthopnea, like dyspnea, is a symptom, and analysis of the pathogenesis of the former is subject to the same above-discussed limitations as the latter. Orthopnea has been classified clinically as "orthopnea of necessity" and "orthopnea of choice" These terms merely distinguish degrees in the feeling of urgency to sit up experienced by patients, that is, degrees of orthopnea itself It is probable that a better term than "orthopnea" is "dyspnea of recumbency." The severity of orthopnea varies considerably from patient to patient, although, in general, it parallels the severity of the degree of dyspnea. The time of onset of the sensation of respiratory distress after lying down varies a good deal; in some instances, the sensation appears immediately and is unbearable from the start; in others, it appears immediately but does not become unbearable for some minutes; in still others, it may never become unbearable The more severe degrees of orthopnea are often associated with a rapid increase of cyanosis of the face on lying down

Changes in blood flow through the lungs.—Lindhard (1913) first

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that such redistributions of blood do occur with changes in position seems to be established. Mills (1944) has shown that the reëntry into the circulation of blood released from an occluded extremity causes brief hyperpnea in normal individuals, and Mackay (1943) reported a sense of suffocation under such circumstances. Mills (1944) concluded that this phenomenon was a consequence of stimulation of pressor receptors in the pulmonary arterial tree, but his experiments are far from conclusive in this regard.

That chemical factors rather than stimulation of pressor receptors account for the hyperpnea and dyspnea occurring after the release of occluded blood is suggested by several observations. large intravenous infusions do not cause dyspnea or hyperpnea (Altschule *et al.*, 1938, 1942); increased respiration following stimulation of pressor receptors should lower the carbon dioxide content of alveolar air, but the release of occluded blood from an extremity is followed by a significant rise in alveolar air carbon dioxide (Mackay, 1943). At any rate, the hyperpnea that may result from redistribution of blood with a shift in position is very brief in duration and wears off as soon as the relatively small excess volume of blood carried to the lungs at one time is redistributed among the thoracic viscera and muscles, the head and neck and the arms It does not seem to be an important factor, for reproducing it by heavy pressure on the engorged liver of congestive failure does not cause dyspnea.

Increased pulmonary congestion —The frequent association of orthopnea and pulmonary congestion has properly led many authors to regard congestion of the lungs as an important factor in the genesis of dyspnea in the recumbent position There has, however, been no general agreement regarding the mechanism whereby pulmonary congestion induces or exaggerates dyspnea in recumbency. A number of authors have stated that dyspnea of recumbency results from increased pulmonary congestion in the recumbent position, consequent to a shift of blood from the lower part of the body (Hill, 1895), pressure on (Reid, 1940) or unfavorable hydrostatic relations within (Dock, 1935) the pulmonary veins, kinking of the pulmonary vessels (Rubow, 1909), or an increase in the volume flow of blood through the lungs in the recumbent position (Field and Bock, 1925, Lawrence *et al.*, 1927, Nielsen, 1936). The last-named cause appears to be ruled out (page 176).

pointed out the decrease in minute volume blood flow through the lungs of normal subjects when they pass from the lying to the sitting or standing position. Many authors have since corroborated this observation (57) The apparently discrepant results of Grollman (1928) and of Schelling and Heinemeier (1933) are due to changes in oxygen consumption which mask the variations in arteriovenous oxygen difference, as Nylin (1934) pointed out. Wide variations in cardiac output with changes in position were noted in studies made with the ballistocardiograph (Starr, 1943; Starr and Rawson, 1941), but the accuracy of these results is questionable. All available data obtained by reliable methods show that in normal individuals the cardiac output relative to oxygen consumption is largest in recumbency, intermediate sitting, and smallest standing. A. V. Bock and his co-workers (Field and Bock, 1925, Lawrence, *et al*, 1927) and Nielsen (1936) regarded the changes that occur in cardiac output when the patient moves from the sitting to the recumbent position as of importance in the genesis of orthopnea, since an increased flow through the lungs in recumbency might cause congestion. The earlier observations (Bielschowsky, 1932; Bock, 1934; Lawrence *et al*, 1927, Mobitz, 1927, Nielsen, 1936) of the effects of changes in posture on the output of the heart in cardiac subjects are fragmentary and difficult to interpret, because many of the patients had only mild failure and some are not described in sufficient detail to permit analysis. However, the more recent experiments of Goldbloom *et al.* (1940) and McMichael (1938*a*, *b*) in patients with moderate or severe failure show that the normal changes do not occur, as is possibly to be expected from the known decreased responsiveness of the cardiac output of patients with congestive failure to other stimuli. Accordingly, it is concluded that the shift in position from sitting to lying does not cause increased blood flow through the lungs. *This conclusion has no bearing on the relief of dyspnea due to the changes that result from prolonged still-standing, or sitting with legs hanging,* which probably consist in some decrease blood volume (page 229).

Redistribution of blood — Although increase in the flow of blood through the lungs does not appear to be a factor in the genesis of orthopnea in cardiac patients, it is possible that the shift of blood into the trunk that occurs when a person changes from the sitting to the recumbent position may cause a brief sensation of discomfort;

marked decrease in lung volume in one orthopneic patient on lying down; this was associated with decreases in reserve air and vital capacity and an increase in complemental air, similar in magnitude to those observed by Altschule *et al.* (1943). McMichael's (1938*b*) finding of a decrease of 50 per cent in the residual air in recumbency suggests some gross error in its measurement, as does the fact that the ratio of functional residual air to total capacity in his patient, which was definitely abnormal in the sitting position, became quite normal in recumbency. Accordingly, his conclusion that an increase in pulmonary congestion occurred in recumbency in that patient cannot be accepted.

Hamilton and Morgan (1932), Hamilton and Mayo (1944), Dow (1939), Mackay (1943), and Campbell and Harvey (1948) felt that the changes in vital capacity that occur in recumbency in normal subjects are related to an increase in the amount of blood in the lungs. However, their conclusions, based on the fact that placing tourniquets on all the extremities resulted in increases in vital capacity of only 3 to 11 per cent, must be considered too sweeping, particularly since they present no analysis of the pattern of changes in the subdivisions of the lung volume in their studies. The fact that application of tourniquets changes the vital capacity slightly, or prevents some of the postural changes, surely does not prove that the changes in lung volume are due to shifts in the distribution of blood.

Changes in respiratory dynamics. — Although no increase in pulmonary congestion in recumbency has been demonstrated, it is not to be concluded that changes in pulmonary dynamics in that position are unrelated to the genesis of orthopnea The decrease in reserve air and increase in complemental air in recumbency in normal subjects were shown by McMichael and McGibbon (1939) to be caused by a cephalad shift of the diaphragm, due presumably to the pressure of the abdominal viscera; this study confirmed the earlier work of Haldane *et al.* (1919) and of Livingstone (1928). The occurrence of similar changes in recumbency in congestive failure also appears to be due to a shift in the diaphragm. Thus, forcing the diaphragm upward by application of an upper abdominal binder in cardiac subjects in the sitting position caused approximately the same decrease in reserve air, without change in the residual air, as did assuming the recumbent position (Altschule *et al*, 1943). The increase in complemental air

The increase in pulmonary congestion by one or more of these factors is believed to induce the dyspnea of recumbency, either by influencing adversely the respiratory exchange (Dock, 1935), by activating reflexes initiated by changes in the parenchyma or blood vessels of the lungs (Dock, 1935; Christie, 1938; Field and Bock, 1925), or by causing increased rigidity of the lungs (Dock, 1935; Christie, 1938). Calhoun *et al.* (1931) and Christie and Beams (1923) found abnormally large decreases in vital capacity in orthopneic patients when the recumbent position was assumed; the findings of the latter are difficult to evaluate, since nonorthopneic patients with congestive failure showed little or no decrease in vital capacity under these circumstances. Harrison's (1933) data are not in agreement with the latter finding

This point was recently reinvestigated (Altschule *et al.*, 1943) by studying the pattern of changes in the subdivisions of the lung volume in recumbent cardiac patients. Congestion of the lungs causes a characteristic change in the relations between various components of the lung volume (page 53): the vital and total capacities are greatly reduced because of corresponding changes in the complemental and reserve airs, and the residual air is somewhat increased. The residual and functional residual air volumes are greatly increased relative to the total lung volume It was felt that a further change in this direction should be detectable if increasing pulmonary congestion occurred on lying down. On the other hand, if no increase in congestion of the lungs occurred in cardiac patients who changed from the sitting to the recumbent position, they would show only the changes associated with recumbency, that is, small decreases in vital and total capacity, diminution in reserve and functional residual airs, no change in residual air, and an increase in complemental air (58; McMichael and McGibbon, 1939). Both orthopneic and nonorthopneic patients with heart disease showed changes which, though smaller, were qualitatively the same as those that occur in normal subjects. Accordingly, it was concluded (Altschule *et al*, 1943) that no measurable change in the degree of pulmonary congestion occurred when the orthopneic or nonorthopneic cardiac patient lay down.

It should be noted that Livingstone (1928) many years ago found the same changes with variation in posture in the lungs of orthopneic cardiacs as in normal subjects. McMichael (1938*b*) reported a

makes it difficult to augment the tidal air, and the aforementioned respiratory inefficiency in recumbency may actually result in a decrease in tidal volume. Lower levels of arterial blood oxygen saturation in the recumbent position, as compared to the sitting position, have been reported by Calhoun *et al* (1931) in patients with congestive failure. These authors reported arterial blood oxygen saturations of 88.6 to 94 0 per cent in the recumbent position in seven orthopneic cardiac patients, without associated pulmonary disease; these levels increased to 93 5 to 98.6 per cent in the upright position in six of the seven cases, the increases ranging between 0 6 and 8.1 per cent In some instances a considerable rise in respiratory rate may occur in recumbency, possibly as a consequence of anoxia, and this increase in respiratory activity may increase the severity of dyspnea. In addition to all these factors there appears to be a greater ease of movement in the upright position, which contributes to the genesis of orthopnea.

Recumbency causes qualitatively the same changes in the respiratory dynamics in normal subjects as it does in patients with congestive failure, indeed, the changes in normal subjects are considerably greater than in patients with congestive failure Nevertheless, orthopnea does not occur in the former and is frequently observed in the latter. Neither the nature of the postural changes in pulmonary dynamics nor their magnitude appears to be responsible for orthopnea in patients with pulmonary congestion Rather, it is the state of respiration and circulation at the time these changes occur which is important in the genesis of orthopnea

Changes in cerebral blood flow. — Ernstene and Blumgart (1930) stressed the importance of changes in cerebral blood flow in the genesis of orthopnea They correlated level of venous pressure with degree of orthopnea and concluded that venous engorgement in the brain might be relieved by sitting up; measurements of jugular pressure by Myerson and Loman (1932) corroborate this conclusion. Of great importance in this connection are the observations of Winsor and Burch (1946) who found that while the venous pressure remained unchanged in normal subjects who moved from the recumbent to the sitting position, the pressure in the veins fell in cardiac patients with this shift in posture In addition, the data of other authors also show that, even in patients with low vital capacities, factors operating outside of the lungs are significant in the genesis of orthopnea. The data

that occurs on lying down could not always be reproduced in these experiments by the application of the upper abdominal binder, which, in contrast to the abdominal viscera, is inelastic and prevents full expansion of the lungs It is worthy of note that the application of the abdominal binder made the patients, normally comfortable when sitting, dyspneic in that position and increased their respiratory minute volumes. It is to be concluded, therefore, that a cephalad shift of the diaphragm, which occurs in recumbency and is due to pressure of the abdominal viscera, is responsible in part for orthopnea

Other authors have shown that the shift in the level of the diaphragm in recumbency results in a decrease in the volume of the functional residual air (Christie and McIntosh, 1934) and an associated lessening of the negativity of the intrapleural pressure in that position (Aron, 1891, 1900, Christie and McIntosh, 1934, Prinzmetal and Kountz, 1934, 1935). The intrapleural pressure in patients with congestive failure is, however, less negative than normal and may be positive during expiration, even in the sitting position (Christie and McIntosh, 1934), further changes in this direction cause increased respiratory embarrassment and inefficiency The claim of Prinzmetal and Kountz (1934) that changes in intrapleural pressure in orthopneic patients are greater than in normal subjects with shifts in position is not supported by the data they presented.

Impaired respiratory function is probably the cause of the smaller tidal volumes in recumbency, as compared to the sitting position, in a majority of orthopneic cardiac patients noted by Calhoun *et al* (1931) and also by others (Altschule *et al.*, 1943). A decrease in tidal air volume in recumbency favors less complete aeration of blood passing through the lungs On the other hand, the relatively small decreases in lung volume and its subdivisions that occur when orthopneic patients lie down indicate that decrease of space available for breathing does not cause orthopnea, as Christie and Beams (1923) and Calhoun *et al* (1931) believed.

When normal subjects change from the sitting to the lying position, respiration is often slowed and the tidal air increases. If this increase in tidal air cannot occur, even normal subjects may develop evidence of anoxemia (Haldane *et al*, 1919) It is, therefore, not surprising that increased dyspnea occurs in many patients with congestive failure in recumbency, since the increased rigidity of their lungs (page 53)

be interpreted, since favorable changes also occur in the lungs and in spinal fluid pressure under these circumstances.

Cerebral venous engorgement appears to be a factor responsible for orthopnea. However, it does not cause orthopnea unless other factors are also operating.

Changes in cerebrospinal fluid pressure. — Increased cerebral venous pressure results in an elevation of cerebrospinal fluid pressure (page 49). Harrison (1933) has expressed the view that this increase in spinal fluid pressure is a primary factor in the genesis of orthopnea, since lumbar puncture relieves the symptom for a time. It is possible that the relief of dyspnea and orthopnea which occurs after removal of spinal fluid is a consequence of a temporary increase in local blood flow related to lowering of intracranial pressure; elevation of spinal fluid pressure is known to slow the cerebral circulation (Shenkin *et al*, 1946).

Mechanical factors. — It is more than likely that mechanical factors are of some importance as causes of orthopnea. The pressure of abdominal viscera, or ascites, or both, on the diaphragm when the patient is recumbent may interfere with its movement to some degree. The occurrence of orthopnea in patients with ascites due to other causes, such as cirrhosis or neoplasm, favors this view. The somewhat greater ease of thoracic movement in the upright position may be important, but is not by itself sufficient to explain orthopnea.

Conclusions — It appears to be valid to regard orthopnea as a consequence of the combined action of a number of factors; additional factors may be present but still unrecognized The occurrence of orthopnea, although influenced profoundly by the above-discussed factors, is conditioned by fundamental changes due to congestive failure. These are (i) increased venous and spinal fluid pressure and (ii) increased rigidity of the lungs and lessened negativity of the intrapleural pressure. It is apparent, therefore, that more marked myocardial insufficiency, or an exaggeration of (i) or (ii) not due to increased failure of the heart, must result in more severe orthopnea as long as the patient remains conscious. Conversely, the relief of orthopnea may be a consequence of improved cardiac function or it may occur as a result of lowered venous or spinal fluid pressures or lessened rigidity of the lungs, independent of changes in cardiac function

of Robb and Weiss (1934) show that, for a given ratio of vital capacity to body surface, patients with peripheral signs of congestive failure, including elevation of the venous pressure, generally exhibit more severe orthopnea than do patients with no peripheral signs of congestive failure and normal venous pressure. Ernstene and Blumgart (1930) pointed out that when orthopneic cardiac patients who are recumbent merely flex the neck forward, orthopnea may be relieved; this maneuver does not change the vital capacity, but does raise the level of the medullary centers with respect to the auricle and facilitates venous drainage. These observations have been corroborated by Calhoun *et al.* (1931) and by Battro and Labourt (1943); the last named also showed that flexing the head forward lowered the respiratory minute volume and did not change the vital capacity.

Altschule and Blumgart (1937) studied a patient with marked engorgement of the face and scalp veins due to tricuspid stenosis. It was found that positions in which collapse of the engorged veins over the face and scalp occurred were associated with relief of orthopnea, whereas engorgement of these veins was always associated with the presence of that symptom. Many authors have reported the occurrence of orthopnea in patients with superior caval obstruction; a recent study (Altschule *et al*, 1945) of this disorder again stresses the role of venous stasis in causing orthopnea Calhoun *et al.* (1931) found increased respiration in normal and cardiac patients with tourniquets about their necks, but respiratory distress did not occur, it is possible that any dyspnea that occurred may have been subordinated to other discomforts brought on by this procedure

An argument advanced against acceptance of the importance of changes in cerebral flow in the causation of dyspnea is the fact that normal subjects do not experience that symptom in the head-down position; actually, however, they do hyperventilate sufficiently to lower the alveolar carbon dioxide content (Donal *et al*, 1934). The validity of this argument is further weakened by the fact that normal persons develop severe respiratory distress when even minimal exertion is attempted in the head-down position (Donal *et al.*, 1934). Relief of orthopnea often occurs after procedures that lower venous pressure, such as venesection (page 227) and administration of diuretics (page 196), are instituted; these phenomena cannot, however,

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has been to study the cardiac output in patients shortly after admission, administer the drug, and then measure the output of the heart again. Many of the patients so studied also received the benefit of other therapeutic procedures, such as bed rest, sedation, limitation of salt and the administration of diuretics, any or all of these may in some of the patients studied have been more important than digitalization itself in securing clinical improvement. In order to control such experiments adequately, further studies of the cardiovascular dynamics should have been made after withdrawal of the drug However, the recent introduction into widespread clinical use of digitalis preparations, which act rapidly, makes this precaution unnecessary.

Almost all authors record a rise in cardiac output or a fall in arteriovenous difference in many or most patients after the administration of digitalis (59, McMichael and Sharpey-Schafer, 1944, Bloomfield *et al*, 1948; Stead *et al.*, 1948). The results of Friedman, *et al.* (1935*a*) are, however, discordant, for they found no change Systematic studies after administration and again after withdrawal of the drug have been carried out by only a few investigators (Ringer and Altschule, 1930; Stewart and Cohn, 1932) and these too show a rise in cardiac output in most patients with cardiac decompensation as a consequence of the action of digitalis In addition, a number of observers have reported an increase in cardiac output in recovery from decompensation (Kroetz, 1930; Seymour *et al*, 1942; Merrill, 1946), and it is probable that most or all of the patients described received digitalis as part of their treatment It appears to be valid to conclude, therefore, that the favorable action of digitalis is associated with a rise in cardiac output. The output of the heart, however, is not always significantly increased and often is not restored entirely to normal; indeed, in some instances the increase is slight — less than 20 per cent This finding should not be surprising, for it is in harmony with clinical experience. Most patients, especially those with auricular fibrillation, show clinical evidence of improvement following the administration of digitalis, but complete clinical recovery is uncommon Most patients with cardiac decompensation experience considerable limitation of activity in spite of digitalization, and many require in addition restriction of salt and repeated administration of diuretics if clinical improvement is to be maintained

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36. *Effects of Therapy. Status of the "Adequately" Treated Patient*

Effects of digitalis. — Many studies have been made of the effect of digitalis on cardiac output or arteriovenous difference in patients with chronic cardiac decompensation, but the available data are difficult to evaluate clearly. In most instances, the procedure followed

stances administered in full doses is primarily a restoration of cardiac output to or toward normal, with a corresponding partial or complete removal of abnormalities in other phases of cardiorespiratory dynamics.

Effects of oxygen. — The administration of oxygen often results in striking relief of dyspnea and may be followed by a diuresis (Barach, 1931; Barach and Richards, 1931; Richards and Barach, 1934). The cardiac output (Barach and Richards, 1931) and vital capacity (Barach and Woodwell, 1921; Katz *et al.*, 1932) are not altered by oxygen therapy, and the venous pressure shows no consistent change (Katz *et al*, 1932) unless diuresis occurs, so that it must be concluded that the effects of the latter are the result of changes which occur in the blood and tissues The arterial (Schoen and Derra, 1930; Barach, 1931; Barach *et al*, 1921, 1931, Cohn *et al*, 1932, Richards and Barach, 1934) and venous (Barach and Woodwell, 1921) blood oxygen saturations rise to or toward normal when patients with cardiac decompensation breathe air enriched with oxygen The respiratory minute volume usually decreases significantly (64, Richards and Barach, 1934), while the expired air carbon dioxide rises (Campbell and Poulton, 1927), according to the last-named authors, however, these changes do not occur in cardiac patients in whom cyanosis is the consequence of a congenital shunt and is not associated with pulmonary congestion.

The decrease in ventilation, consequent to oxygen therapy, results in a rise in carbon dioxide content in the arterial blood (Barach, 1931, Barach *et al.*, 1921, 1931; Cohn *et al*, 1932; Richards and Barach, 1934), but the blood pH is not changed markedly (Barach and Richards, 1931). Decreases in blood lactate occur as a consequence of relief of anoxia (Barach, 1931; Barach and Richards, 1931; Jervell, 1928). Related to this phenomenon is the observation that carbon dioxide output during exercise is increased in patients with cardiac decompensation breathing air containing high concentrations of oxygen (Campbell and Poulton, 1927) If diuresis occurs as a consequence of the administration of oxygen, it is accompanied by the changes usually associated with it (page 195), namely, increased urinary excretion of chloride, fall in plasma chloride, rise in plasma protein and fall in venous pressure.

Emphasis must be laid upon the fact that the small degrees of

It is necessary to have in mind clearly the significance of the effect of digitalis in increasing cardiac output. Many other factors, such as oxygen lack and anemia, increased venous return, elevation of metabolism with exercise, fever, thyrotoxicosis and utilization of food, acidosis, anxiety, the injection of adrenalin, also increase cardiac output. In patients with damaged myocardium these factors constitute an additional strain on the heart and are, therefore, harmful. Digitalis, on the other hand, increases the cardiac output and thereby benefits the entire body, but the heart is not put under any deleterious burden; increase in cardiac output is associated with or caused by an improvement in the metabolism of the cardiac muscle itself, that is, an increase in efficiency.

Data on the effect of digitalis on peripheral blood flow in patients with congestive failure are scanty. No change was found by Eichna and Taube (1943, 1944) in the flow through the hand or calf; data on possible changes in metabolic rate were not reported by these authors, however. Stewart *et al.* (1946) reported a considerable increase in the peripheral circulation as a whole after digitalization. All observers agree that digitalization shortens the circulation time (**60**; Stewart *et al*, 1938, 1946, Wood, 1940) and lowers the venous pressure (**61**; Stewart and Cohn, 1932; Kinsman and Moore, 1935); in the case of digitalis preparations, which act rapidly, it is possible to demonstrate that the fall in venous pressure precedes diuresis (Eichna and Taube, 1944) The right auricular pressure also falls (Howarth *et al*, 1947), as does the peripheral resistance also (Howarth *et al*, 1947; Bloomfield *et al.*, 1948).

After digitalization the vital capacity becomes increased (**62**; Friedman *et al*, 1935*a*). The respiratory minute volume decreases (**63**; Boyer and Bailey, 1943), and alveolar carbon dioxide content rises (Ringer and Altschule, 1930, Smith *et al*, 1930). The basal metabolic rate also falls (Grassman and Herzog, 1932; Ringer and Altschule, 1930; Stewart *et al.*, 1946) After exercise the oxygen debt is lower in a patient who has been digitalized than in the same patient before administration of the drug (Nylin, 1939). The blood volume diminishes after administration of digitalis (Ewig and Hinsberg, 1931; Brandt, 1931; Mies, 1931); the claim of Mies (1931) that the blood is merely driven into hidden depots appears to be unfounded.

It appears, therefore, that the effect of digitalis or similar sub-

ciable dosage, it raises the plasma chloride level somewhat (65, Dennig *et al*, 1929)and the changes that occur in the plasma are reflected in edema fluid (Gilligan *et al*, 1934) but not in the spinal fluid (de Thurzo and Katzenelbogen, 1935) There also occurs a marked increase in urinary chloride (66, Dennig *et al*, 1929) and an increase in urinary acid (Keith and Whelan, 1926, Dennig *et al.*, 1929) Considerable, though lesser, amounts of body base are excreted with chloride (67; Gamble *et al*, 1925), most of the base consisting of sodium, with smaller amounts of potassium and calcium The electrolyte pattern of the urine during the administration of ammonium chloride indicates that appreciable amounts of extracellular and small amounts of intracellular fluids are being excreted (Gamble *et al*, 1925; Keith and Whelan, 1926; Dennig *et al*, 1929) When given in large doses, ammonium chloride causes a decrease in plasma volume with evidences of hemoconcentration, that is, a rise in plasma protein level, in normal individuals (Lyons *et al*, 1944*b*) It is important also that the changes in electrolyte balance (Dennig *et al*, 1929; Ethridge *et al*, 1936) and in plasma volume (Lyons *et al*, 1944*b*) induced by continuous administration of ammonium chloride reach a maximum in three or four days and then become less marked

When used in moderate or large doses, ammonium chloride lowers the blood bicarbonate level (68, Barach *et al.*, 1946) and in doses of 8 Gm or more a day, it may lower the blood pH (69, Barron *et al.*, 1937); smaller doses do not affect the pH (Dennig *et al.*, 1931) Lowered blood pH is accompanied by an increased respiratory minute volume (70; Følling, 1929) and lowering of the alveolar (71, Haldane, 1921) and arterial (72, Keith and Whelan, 1926) carbon dioxide contents, the arterial blood oxygen saturation may fall slightly (Cullen *et al*, 1931) or remain unchanged (Barach *et al.*, 1946) * The increased respiratory activity that the drug causes when given in large doses may make patients with congestive failure more uncomfortable Indeed, it has been shown that as little as 7 5 Gm per day appreciably reduces the potential oxygen debt, that is, the ability to do work, in normal individuals (Dennig *et al*, 1931) Smaller doses may have a similar effect in cardiac patients.

* These changes refer to conditions at sea level and have no bearing on the disputed effectiveness of ammonium chloride in relieving altitude sickness (Barach *et al*, 1946, Barron *et al*, 1937)

arterial blood deoxygenation that commonly obtain in patients with cardiac decompensation give no accurate indication of the possible beneficial effects to be derived from oxygen therapy. The biological action of oxygen depends not on saturation directly but on the oxygen tension Thus, while in normal subjects the arterial blood oxygen tension is in the neighborhood of 100 mm-of-mercury and the blood is over 95 per cent saturated, when 100 per cent oxygen is breathed, the percentage saturation increases only slightly but the tension rises to approximately 700 mm-of-mercury. This phenomenon is explainable by the fact that additional oxygen is carried in physical solution in the plasma, the amount of dissolved oxygen being determined by the percentage of that gas in the alveolar air. It is apparent that although the arterial blood oxygen tension in patients with congestive failure is usually somewhat below the normal, exposure to high oxygen tensions in the air breathed charges the blood with large amounts of dissolved oxygen. Further, even in those patients in whom no deficit of arterial blood oxygen exists, the addition of dissolved oxygen makes more of that gas available to the tissues, so that the capillary blood becomes less markedly deoxygenated than it would otherwise be.

On the other hand, prolonged exposure to very high oxygen concentrations, that is, in the neighborhood of 100 per cent, in the inspired air, has certain deleterious effects Since the nitrogen in the lungs is washed out, atelectasis is favored, moreover, the gas in high concentrations is irritating to the lungs (Watt *et al.*, 1943; Bean, 1945). In high concentrations oxygen has a vasoconstricting effect on the cerebral vessels and the flow through the brain falls (Behnke *et al.*, 1935; Kety and Schmidt, 1946). The cardiac output is also somewhat diminished (Otis *et al.*, 1946; Whitehorn *et al.*, 1946). These deleterious effects can be avoided without sacrificing too much of the beneficial action of high oxygen tensions by the use of mixtures containing 60 or 70 per cent of oxygen.

Effects of diuretics — (1) *Ammonium chloride diuresis.* Ammonium chloride is commonly regarded as a diuretic drug, which it is when given in fairly large doses, that is, more than 5 Gm. per day. In smaller doses it has no significant diuretic action, nor does it ordinarily enhance the action of mercurial diuretics (Goldring, 1929; Berglund and Sundh, 1935; Ethridge, 1936). When given in appre-

Gm. five times a day for two days, beginning the day before a mercurial diuretic is to be injected.

(2) *Mercurial diuretics.* Although the chemical methods used in studying diuresis are far more accurate than the physiologic methods used in studies on circulation and respiration, there is much more disagreement concerning the mode of action of diuretics than in any other branch of cardiovascular physiology. The literature on the action of mercurial diuretics is large and confusing. Many of the reported studies are meticulously done, but an equally large number, particularly those dealing with the initial changes, appear to be blended of a smattering of observations and much a priori reasoning.

(*a*) *Consequences of diuresis.* (i) *Urine chloride and base excretion.* Almost the only point agreed upon by all workers is that the injection of a mercurial diuretic in normal or edematous animals or men is followed by the formation of an increased volume of urine, which, though of a lower specific gravity than control specimens, has a higher concentration of chloride, so that a very large output of chloride results (**73**, Blumgart *et al*, 1934, 1936) There is a smaller increase in the output of base (**74**; Herrmann and Decherd, 1937), chiefly sodium, with considerably smaller amounts of potassium and calcium excreted There is a constant relation between the chloride, water and base excreted in edematous cardiac patients (Blumgart *et al.*, 1936) as well as normal individuals (Blumgart *et al*, 1934). Mercurial diuretics cause the loss of larger amounts of chloride than do any of the other diuretic substances Following the diuresis a period of retention of chloride and base is observed

(ii) *Late changes in plasma electrolytes* The marked excretion of chloride leads to a lowering of plasma chloride late in and following the period of diuresis (**75**, Herrmann *et al*, 1932*a*, *b*) The decrease in plasma chloride level is most marked in edematous subjects since it varies with the diuresis It is prevented by the simultaneous administration of 7 to 10 Gm per day of ammonium chloride (Blumgart *et al*, 1936). Simultaneously with the fall in plasma chloride, there usually occurs a corresponding rise in plasma bicarbonate The plasma sodium level is usually unchanged (Keith and Whelan, 1926; Blumgart *et al*, 1936; Herrmann and Decherd, 1937), although occasional decreases occur (Blumgart *et al*, 1936), a slight rise in plasma potassium has also been noted (Nothmann, 1933). The washing out

Another deleterious effect of the use of ammonium chloride in large doses is the increase in cardiac output that it causes. This increase is due mainly to decreased carrying capacity for carbon dioxide and also to some extent to increased oxygen consumption, associated with hyperventilation (Norlin, 1933). The large doses of the drug required to make its diuretic action significant may often result in nausea or other signs of gastro-intestinal irritation. Impairment of utilization of vitamin C may occur (Hawthorne and Storvick, 1948). In addition, continued acidosis may possibly increase catabolism of body proteins (Mackay *et al.*, 1941).

There appears to be little justification for the use of ammonium chloride in large daily doses as a diuretic in the treatment of edema of congestive failure, these doses impair respiratory mechanisms, increase cardiac work, and may cause gastro-intestinal upsets and protein wastage. The use of small doses — 1 to 3 Gm. a day — is also not recommended. These small doses do not have a significant diuretic effect. The action of ammonium chloride as a diuretic, when given in small doses, depends largely upon its making available chloride for the purpose of carrying off sodium from the body. Since only a portion of the ingested ammonium chloride is so utilized, it is to be expected that a dose of 3 Gm , for instance, would result in the excretion of the sodium contained in only 200 cc. of edema fluid.

Ammonium chloride is nevertheless useful in the treatment of edema when used together with more potent diuretics. Since the volume of a diuretic response depends to a large extent on the plasma chloride level (page 196), it is apparent that ammonium chloride may sometimes enhance the action of more potent diuretic drugs by raising the plasma chloride level in patients who exhibit a diminished response to mercurial or xanthine diuretics as a consequence of low plasma chloride level. This low level may be the result of the combined effects of prolonged rigid salt deprivation and of frequently induced diuresis. This hypochloremia is particularly likely to occur in patients who repeatedly receive mercurial diuretics (page 195). Blumgart, Gilligan and Volk (1936) have shown that the administration of 7 to 10 Gm. of ammonium chloride prevents the fall in plasma chloride level that otherwise occurs as a consequence of the action of mercurial diuretics. A reasonable plan, therefore, for the use of ammonium chloride in the treatment of cardiac edema is to give 1 to 2

chloride (Berglund and Sundh, 1935; Evans, 1936; Reaser and Burch, 1946) minimizes or altogether prevents diuresis following the injection of mercurial diuretics. In such instances restoration of chloride levels by means of ammonium chloride (page 193) restores the effectiveness of such diuretics. An interesting experiment was performed by Goldring (1929) in two patients no longer responsive to mercurial diuretics because of low plasma chloride levels. He gave 5 Gm. of sodium chloride daily for three days, during which time the patients gained several pounds of edema fluid, plasma chloride levels rose. When, however, another injection of salyrgan was given, the resultant diuresis carried off all the fluid gained and in addition very much more. A similar result was reported by Berglund and Sundh (1935). The marked chloride losses associated with diuresis by mercurials may lead to lowering of plasma chloride and refractoriness to diuretics if combined with rigid restriction of soduim chloride intake; it is obviated by avoidance of too rigid restriction of salt in the diet or by the use of ammonium chloride (page 193) Similarly, depletion of body sodium leads to unresponsiveness to subsequent injections of mercurial diuretics (Weston and Escher, 1948)

(*b*) *Mechanism of diuresis.* (i) *Early changes in plasma electrolytes.* Changes in plasma electrolytes during the first few hours after the injection of mercurial diuretics, that is, before the onset of the diuresis, have been studied in an attempt to ascertain whether chloride or water is mobilized from the tissues The results are widely discrepant Early rises in plasma chloride in animals and human subjects have been found by some (78, Stockton, 1936) and have led to the conclusion that mercurials act by mobilizing chloride from tissue fluid into blood. On the other hand, an early fall in plasma chloride (Nonnebruch, 1921, Crawford and McIntosh, 1925, Herrmann *et al*, 1932*a*, *b*) observed by others has led to the conclusion that water is mobilized from the tissues Still others have found the early changes in plasma chloride to be variable and inconstant (Claussen, 1932; Bouyoucous, 1934), while excellent work has been done that shows no early change at all (79, Blumgart *et al*, 1934, 1936; Fulton *et al.*, 1934). It is concluded that no early changes in plasma electrolytes occur before the onset of the diuresis due to mercurials.

(ii) *Early changes in plasma protein and erythrocyte mass.* A fall in plasma protein within a few hours after injection of mercurials and

of large amounts of calcium with resulting tetany described by Nothmann (1932) has not been found by any other observer.

(iii) *Late changes in plasma protein.* The plasma protein level at the end of the diuresis (76; Calvin *et al.*, 1940*a*, *b*) in normal or edematous animals or men is often found to be elevated above the control value. The finding of de Vries (1946) that mercurial diuresis causes a rise in plasma protein level only in the absence of edema is discordant The plasma specific gravity (Blumgart *et al.*, 1936) and colloid osmotic pressure (Bryan *et al.*, 1935; Claussen, 1932; Meyer, 1931) show changes parallel with those in plasma protein level A slight rise in the ratio of albumin to globulin has also been reported (Claussen, 1932, Calvin *et al.*, 1940*a*, *b*).

(iv) *Late changes in the tissues.* The edema fluid shows changes in electrolytes corresponding to those that occur in the blood (Crawford and McIntosh, 1925, Gilligan *et al*, 1934). The protein content of the edema fluid rises (page 97) The tissue pressure falls (Burch and Sodeman, 1937) as diuresis proceeds.

(v) *Late changes in blood volume.* The plasma and blood volumes are decreased considerably at the end of diuresis in normal or edematous animals or men (77. Lyons *et al*, 1944*a*, 1946). The more variable results recorded by Swigert and Fitz (1940) and by Spühler *et al.* (1948) are discordant. Plasma and total red cell volume decrease approximately in proportion, the hematocrit varying a little in either direction (Cardozo, 1939; Goldhammer *et al.*, 1935) although small rises are perhaps more common (Crawford and McIntosh, 1925, Keith and Whelan, 1926; Lyons *et al.*, 1944*a*, 1946; de Vries, 1946).

(vi) *Late changes in circulation* The cardiac output is unchanged (Friedman *et al.*, 1935*b*), but the venous pressure falls (Lyons *et al*, 1944*a*, Volini and Levitt, 1939, 1940) and with it the cerebrospinal fluid pressure (Volini and Levitt, 1940). Swigert and Fitz (1940) found variable changes in venous pressure and circulation time. Congestion in the lungs appears to be somewhat ameliorated, for the vital capacity increases by a few hundred cubic centimeters (Alsever and Levine, 1938, Swigert and Fitz, 1940)

(vii) *Variations in the volume of diuresis; role of salt.* A low plasma chloride level (Bouyoucous, 1934; Evans, 1936; Goldring, 1929; Keith and Whelan, 1926) or the previous depletion of body

the injection of larger amounts into a renal artery results in oliguria. The cross-circulation experiments of Govaerts (1928), using one animal given a mercurial diuretic into the renal artery and another not so treated, afford convincing evidence of the renal site of action of mercurial diuretics. Mercurial diuresis is inhibited by BAL (Farah and Maresh, 1948) and also by morphine (Ferrer and Sokoloff, 1947).

It appears that the action of the mercury in mercurial diuretics slightly impairs tubular function without otherwise damaging the kidney, so that the reabsorption of chloride is diminished and a large loss of chloride, water and base is initiated

(3) *Xanthine diuretics.* A large number of substances fall into the group of xanthine diuretics. There is no conclusive evidence that the action of all of them is similar, but for the purposes of discussion they have been grouped together.

(*a*) *Consequences of diuresis.* (i) *Urinary chloride excretion.* The occurrence of diuresis following the injection of xanthine diuretics of various types is associated with an increase in urine chloride content and total output (83; Blumgart *et al*, 1934, Fulton *et al.*, 1934); the changes are not as striking as those that occur with mercurial diuresis. The excretion of base is increased also (Blumgart *et al.*, 1934; Herrmann *et al.*, 1932*a*, 1937; Keith and Whelan, 1926, Threefoot *et al*, 1947; Fowell *et al.*, 1948). There is a parallel excretion of base, chloride and water (Blumgart *et al*, 1934).

(ii) *Late changes in plasma chloride* Some decrease in plasma chloride level late during or after the period of diuresis has been reported (Moller, 1927; Fulton *et al.*, 1934) although Stockton (1936) reported a slight rise, Herrmann *et al.* (1932*a*) observed fluctuations and Blumgart *et al.* (1934, 1936) no change in normal subjects or edematous cardiacs. The blood sodium level is described by all authors as unchanged (Blumgart *et al.*, 1934, 1936, Herrmann and Decherd, 1937).

(iii) *Late changes in plasma protein and hemoglobin* Increased plasma protein levels were found at the end of diuresis by Calvin *et al.* (1940*b*), but lowered levels for plasma protein and plasma colloid osmotic pressure were described by Meyer (1931*b*). On the other hand, the hemoglobin level (Moller, 1927) and plasma specific gravity (Stewart, 1941) have been reported as increased after the

before or with the onset of diuresis has been reported by some observers (80, Claussen, 1932) and has been taken to indicate hemodilution by mobilization of water from the tissues. Similar changes in plasma colloid osmotic pressure (Kylin, 1932; Meyer, 1931a) and red cell count (Bohn, 1923) or hematocrit (Simmert, 1935) have been interpreted in a similar fashion. However, some authors describe early elevation of plasma protein (Schally, 1935) or colloid osmotic pressure (Oelkers, 1931) with a rise in the ratio of albumin to globulin (Schally, 1935), which is interpreted as indicating transfer of albumin from the tissues into the blood together with a lesser amount of water. The hematocrit is also said to be variable (Feher, 1929; Petersen, 1940). The best work indicates that no dilution occurs (Bleyer, 1922; Bryan *et al*, 1935; Schmitz, 1933).

(iii) *Early changes in plasma volume* Feher (1929) reported an early increase in plasma volume, but Levin (1941) and Evans and Gibson (1937) found it unchanged.

(iv) *Studies of renal function Conclusions.* The urea clearance is unchanged during mercury diuresis (Fulton *et al.*, 1934; Page, 1933) or slightly decreased (Herrmann *et al.*, 1933); studies of inulin or creatinine clearance have shown no change in glomerular filtration (81; Farnsworth, 1946) Chloride clearance is, however, greatly increased (Farnsworth, 1946), and reabsorption of chloride is markedly decreased (82; Herrman *et al*, 1932*a*, *b*, 1933, 1937; Blumgart *et al*, 1934, 1936). Sodium clearance also rises (Threefoot *et al.*, 1947). This phenomenon appears to be the mechanism of diuresis following the administration of mercurials, for although reabsorption of water is also decreased (Farnsworth, 1946), loss of body salt precedes loss of body water in diuresis so induced (Reaser and Burch, 1946). Attempts also have been made to show that an increase in insensible water loss contributes to the disappearance of edema, but the observed results are variable and not convincing (Gabriel and Kahler, 1934; Magendantz and Stratman, 1933). Bartram (1932) found that the injection of small amounts of mercurial diuretics directly into a renal artery caused an immediate increase in the flow of a dilute urine from that side, with a later smaller increase in urine volume from the other kidney. Melville and Stehle (1927) performed similar experiments, but did not observe this response, probably because of the injection of too large a dose, for Bartram (1932) also showed that

the blood stream from the tissues. An early lowering of colloid osmotic pressure is, however, described (Kylin, 1932) in rabbits. Early decreases in hemoglobin (Möller, 1927) and in plasma specific gravity (Stewart, 1941) have also been noted

(iii) *Early changes in plasma volume.* A rise in plasma volume was noted by Calvin *et al.* (1940*a*) early in the course of xanthine diuresis.

(iv) *Studies of renal function. Conclusion.* The urea clearance is described as unchanged (Fulton *et al.*, 1934, Page, 1933) or increased (Herrmann *et al*, 1933). Glomerular filtration is described as increased in man by Herrmann *et al.* (1932*a*, *b*, 1933, 1937), Chasis *et al* (1938), Escher *et al.* (1948), and Fowell *et al* (1948), and in dogs by Schmitz (1932); Blumgart *et al* (1934) found it unchanged in normal man, and Berglund and Sundh (1935) found the changes equivocal. No change was found in rabbits (Forster, 1947). Reabsorption is described as unchanged (Schmitz, 1932) or variably diminished (Blumgart *et al.*, 1934, Herrmann *et al.*, 1932*a*, *b*; Forster, 1947). The injection of xanthines into a renal artery in dogs yielded diverse responses (Bartram, 1932), theobromine sodium acetate acted much like mercurials in that an immediate increase in urine flow from the injected kidney resulted, but theobromine sodium salicylate, theobromine calcium salicylate and aminophylline caused no such response but rather a delayed bilateral diuresis. It is apparent that the available data are too contradictory to permit of any conclusion as to the mechanism of action of the xanthines. However, as with all substances that have diuretic effects, their action is associated with an outpouring of chloride and lesser amounts of base The changes are less marked than those induced by mercurials.

(4) *Digitalis as a diuretic.*—The diuresis that follows the administration of full doses of digitalis in a patient with congestive failure is apparently related to the improvement in circulation that results (page 189); an increase in renal blood flow (Herrmann *et al.*, 1932*a*; Merrill, 1946) has also been noted Urea clearance (Herrmann *et al.*, 1933) and glomerular filtration are increased (Herrmann *et al.*, 1932*a*, *b*, 1933) little or no change occurring in tubular reabsorption. The urine chloride concentration and total output rise (Falta and Quittner, 1917; Herrmann *et al.*, 1932*b*, 1933; Keith and Whelan, 1926; Steyrer, 1902; Stockton, 1932) and there is also an increased

diuresis. It is probable that, after a diuresis due to the xanthines, some hemoconcentration occurs.

(iv) *Late changes in plasma and blood volumes.* The plasma and blood volumes are decreased after xanthine diuresis, according to Calvin *et al.* (1940*a*) and Fowell *et al.* (1948).

(v) *Changes in circulation.* Friedman *et al.* (1935*b*) and Berseus (1945) found no lasting change in cardiac output after administration of xanthine diuretics, but Stewart and Cohn (1932) reported a significant persistent rise. Hoen (1936), Starr *et al* (1937), Howarth *et al.* (1947), Escher *et al.* (1948) and Fowell *et al.* (1948) observed increases in cardiac output shortly after the injection of theophylline, and Stewart and Jack (1940) also found a considerable increase in peripheral blood flow in similar experiments. This change was, however, of short duration in the study of Stewart and Jack (1940) and probably explains the untoward reactions to that drug more than it does anything else, additional discussion along these lines is given elsewhere (page 223).

(vi) *Role of chloride in diuresis.* As in the case of mercurial diuretics, little or no diuresis will occur with xanthine when the plasma chloride is low (Curtis, 1927, 1929). Similarly, the administration of chloride enhances xanthine diuresis; Frandsen and Møller (1928) gave saline solution to rabbits before the injection of a xanthine diuretic and noted a diuresis that contained the volume of saline solution given and a good deal more in addition.

(*b*) *Mechanism of diuresis.* (i) *Early changes in plasma chloride.* A rise of plasma chloride level after the injection of a xanthine diuretic, but before the onset of diuresis, has been described in rabbits (Curtis, 1925, 1929; Möller, 1927); this was taken to indicate mobilization of chloride from the tissues. However, an early fall was found in man (Stockton, 1936) and no consistent change in other experiments on rabbits (Möller, 1927), dogs (Hansen *et al.*, 1931), and human subjects (Blumgart *et al*, 1934; Fulton *et al.*, 1934; Herrmann *et al.*, 1932*a*).

(ii) *Early changes in plasma protein and hemoglobin.* Decreased plasma protein levels were found by Calvin *et al.* (1940*b*) shortly after the injection of xanthines, however, Meyer (1931*b*) found increased plasma protein and oncotic pressure at this time. Meyer (1931*b*) considered that the latter indicated transfer of protein to

decompensation are faulty because they emphasize only one aspect of the problem. The Karell diet, namely, 800 cc. of skim milk daily, should not be used for any length of time because it restricts fluids to an undesirable degree and is deficient in calories, thiamine, protein, and iron (Harrison, 1945). Starvation as a form of therapy in congestive failure is undesirable, since the published data show that it depletes the protein stores (Proger and Magendantz, 1936). Diets that limit salt intake to an extreme degree are generally unpalatable and are deficient in protein and often thiamine also. Many of the regimens suggested, including the acid-ash diet, are too complex to be used by the patient at home The effects of the acid-ash diet can be secured with much less trouble by giving suitable quantities of ammonium chloride.

The diet for a patient with cardiac decompensation should be adequate in regard to calories and of high protein and vitamin B content Since many of these patients are anoretic (Harrison, 1945), the diet should be varied, palatable, attractively prepared and concentrated in bulk Salt intake should be limited to a moderate degree; little or none should be added in cooking, and none at the table In the case of patients who are very ill, and in whom the rise in cardiac output that occurs with large food intake (Grollman, 1929) is undesirable, a regimen of six small meals per day may be helpful. Fluids should be adequate in amount, forcing fluids has no benefit (Gorham *et al*, 1947).

The effects of such measures as venesection, injection of morphia, application of tourniquets, still-standing or sitting with feet dependent, and the use of positive-pressure apparatus are discussed elsewhere (page 224).

Physiologic status of the "adequately" treated cardiac patient. — A group of patients was studied some years ago in order to determine the physiologic status of the patient with chronic cardiac decompensation in whom the greatest possible improvement in symptoms was secured by treatment in the hospital (Altschule, 1938). These patients received the benefit of complete bed rest for several weeks, limitation of salt, full doses of digitalis, adequate diuresis with mercurial preparations, and in a few instances venesection or oxygen therapy as well. It was evident that striking symptomatic improvement had occurred, there was no edema and at most minimal

excretion of base (Steyrer, 1902; Keith and Whelan, 1926). These derive mainly from the extracellular fluid. Variable changes in plasma chloride level were recorded by Herrmann *et al.* (1932*a*, *b*), while other authors have reported that a fall in plasma chloride follows the diuresis (McLean, 1915; Stockton, 1932). The diuresis is followed by a decrease in plasma volume (Calvin *et al.*, 1940*a*; see also page 108) and a rise in plasma protein (Calvin *et al.*, 1940*b*) and specific gravity (Stewart, 1941). A slight initial rise in plasma volume (Calvin *et al.*, 1940*a*), accompanied by a decrease in plasma protein (Calvin *et al*, 1940*b*) and specific gravity (Stewart, 1941), has been interpreted as evidences of mobilization of fluid from the edematous tissues, further studies will have to be made before this conclusion can be accepted.

(5) *Oxygen as a diuretic.* — Occasionally edema disappears when the patient is given oxygen and reappears when the administration of oxygen is discontinued (Barach, 1931; Barach and Richards, 1931; Richards and Barach, 1934). The diuresis that occurs under such circumstances is accompanied by an increased urinary chloride excretion, a fall in plasma chloride level and a compensatory rise in bicarbonate concentration, according to these authors. The diuresis is followed by a rise in plasma protein level.

Effects of rest — Bed rest not only serves the obvious purpose of reducing activity to or toward a level that the heart can support, but it is also important because it enables patients who are in a continuous oxygen debt (page 93) to discharge that accumulated debt. Studies of the effects of bed rest in patients with congestive failure are scanty; the data of Kinsman and Moore (1935) show some fall in venous pressure and in a few cases slight acceleration of circulation time; Hussey (1936) also stressed the rapid fall in venous pressure which may occur with bed rest. In view of the known effects of activity and of straining on the venous pressure (page 36), it is to be expected that the rest and relaxation which the patient experiences after being put to bed will have this effect. An attempt should be made to ascertain whether bed rest alone can, after a time, so rest the heart as to enable it to recover somewhat and show an increase in output relative to the body's metabolic needs.

Role of diet. — The dietary management of cardiac patients is of great importance, but many of the diets suggested for use in cardiac

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dyspnea at rest. However, evidence of the persistence of an abnormal cardiovascular physiologic condition was shown by the somewhat decreased cardiac output, tendency toward an increased respiratory rate and minute volume, a slight decrease in arterial blood oxygen saturation, a lowering of the vital capacity, a prolongation of the pulmonary circulation time, and, in one patient, slight elevation of the venous pressure. These findings corroborated and extended the observations of other authors who have studied the cardiovascular system after recovery from congestive failure and have been corroborated by others since (Ferrer *et al*, 1948). The persistence of physical abnormalities, such as cyanosis, cardiac enlargement and hepatic enlargement in the cases reported (Altschule, 1938), is to be noted. *The symptoms of dyspnea, orthopnea and edema were controlled but the results of the cardiovascular physiologic measurements in each case failed to return to normal values.* Following discharge from the hospital all of the patients, except one who died, returned with fully developed cardiac decompensation within a year, in spite of the fact that their activities were markedly limited. It is clear that the improvement they experienced as a result of their hospital stay was due to the treatment of the secondary consequences of an inadequate cardiac output, as well as to an increase in the minute volume output of the heart; the latter, however, did not reach normal levels even with the patient at rest in bed.

This result explains not only the physiologic findings but the clinical course in chronic cardiac decompensation. Some patients, especially those with mild or moderate cardiac decompensation, find a level of activity at which they can avoid the signs and symptoms of congestive failure without much active treatment. In other cases, particularly those with more severe degrees of failure, continuous treatment, such as the frequent use of diuretics and repeated hospitalization, is necessary in spite of marked limitation of the patient's activity.

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Chapter I — Section 36

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37. *"Backward" Failure. "Forward" Failure. A Generalization Concerning the Pathogenesis of the Signs and Symptoms of Congestive Heart Failure*

It is evident from all of the foregoing discussion that chronic cardiac decompensation is associated with a large number of complexly interrelated bodily changes. That other changes, as yet unrecognized, may occur is likely.

A low cardiac output is the rule in cardiac decompensation that is not complicated by anemia, fever, thyrotoxicosis, acidosis, cor pulmonale, severe thiamine deficiency, and so on. The few reported studies in which a normal cardiac output was found in the absence of these complicating diseases included patients in whom were found elevated metabolic rates as high as plus 85 per cent consequent solely to congestive failure itself. It is clear that under these circumstances the cardiac output is low in proportion to the metabolic needs of the body. The disproportion between circulation and metabolism in congestive failure is greatly aggravated by exercise, a factor which is responsible for increase in symptoms in all patients with myocardial insufficiency. Most patients with congestive failure have elevated venous pressures. The normal response to such increases in venous pressure is a considerable increase in cardiac output, but decompensated patients do not exhibit this response.

The widespread physiologic changes in congestive failure are all probably secondary to a cardiac output that is low in relation to the metabolic needs of the body and to the venous return. It must be borne in mind, however, that some of these secondary changes may overshadow the lowering of the cardiac output as the direct cause of one symptom or another in some patients. Thus, in some instances, intrapulmonary changes may be more important in the genesis of dyspnea, or lowering of the plasma protein level more important in the genesis of edema, than anoxemia consequent to an inadequate cardiac output. The low cardiac output of congestive failure may give rise to the signs and symptoms of cardiac decompensation in many ways. All or nearly all of these different mechanisms are present in all patients with congestive failure, but one or another may predominate in a given patient, or several may be equally important.

This concept is not new and has been expressed in various terms by other authors. Particularly pertinent is the conclusion of Weiss and Ellis (1930) that "evidence is available that a number of mechanisms are responsible for the clinical manifestations of cardiovascular diseases. Confusion exists, nevertheless, because results of experimental and clinical studies of a single aspect of the circulation are still offered as an explanation or index of the multiform nature of circulatory failure."

Any theory that attempts to explain the origin of all the signs and symptoms of congestive failure as *directly* consequent to "forward" failure (low cardiac output) or "backward" failure (increased peripheral and pulmonary venous pressures) is clearly inadequate. Back pressure can occur only if the blood fails to go forward; moreover, failure of the blood to go forward must result in back pressure, provided the volume of circulating blood does not decrease An additional criticism of both theories is that both neglect the chemical changes that are potent factors in the genesis of various signs and symptoms of cardiac decompensation.

As stated previously (Altschule, 1938), a valid generalization concerning the origin of the signs and symptoms of chronic congestive failure is that they are due to summation of the effects of submaximal or even minimal changes in a multiplicity of complexly interrelated factors and that the degree of change in each of these factors, and consequently their importance, varies from patient to patient. The fundamental defect, however, is a cardiac output which, in relation to the metabolic requirements of the body and to the venous return, is abnormally lowered.

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Chapter I — Section 37

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II

ACUTE PULMONARY EDEMA. CARDIAC ASTHMA

The syndromes of acute pulmonary edema and cardiac asthma in patients with heart disease are considered by most clinicians to be caused by sudden weakening of the left ventricle, while the right ventricle continues normal function, at least for some time. This view receives little, if any, support from physiologic studies and is not accepted by physiologists; studies in animals, such as those of Modrakowski (1914) and those reviewed by Luisada (1940) by Henneman (1946), and by Cameron (1948), throw much doubt on the concept. The reviews of Luisada (1940), Henneman (1946) and Cameron (1948) bring forward strong evidence for the view that pulmonary edema, such as occurs acutely in patients with heart disease, is the consequence of a vasomotor disturbance of the pulmonary circulation initiated by neurogenic factors. For the purposes of the present discussion, pulmonary edema will be considered a syndrome caused by mechanisms whose nature has not yet been established.

Cardiac output. — Lauter's (1930) observations in three patients, using cardiac puncture to obtain blood for estimating arteriovenous oxygen difference, showed that the blood flow through the lungs, that is, the output of the right ventricle, was diminished. That of the left ventricle was, therefore, also decreased in these patients. Weiss and Robb (1933) used the dye method to measure cardiac output and found it to be unchanged or decreased during the attack; however, some of their patients had low cardiac outputs and increased arteriovenous oxygen differences (measured by means of blood drawn from the femoral artery and vein) between attacks. Their data are

not presented in detail; consequently it is impossible to analyze them further here. Moreover, the dye method used by them to estimate cardiac output is less accurate than the other methods commonly used. A tentative conclusion, based on scanty data, is that the output of both ventricles is decreased during the attack.

Circulation time. — The arm-to-tongue or arm-to-face time is uniformly reported increased in patients with cardiac asthma (1; Plotz, 1939). Stead and Ebert (1942), in a discussion of the shock syndrome in patients with heart disease, reported studies of patients in shock who also had pulmonary edema; the circulation time was increased to the same degree as in the other reported instances of edema of the lungs. According to Oppenheimer and Hitzig (1936), the arm-to-lung time, as measured by means of ether, is normal, but Plotz (1939) found it to be increased in two-thirds of his patients during attacks The arm-to-tongue or -face time is also increased *between* attacks (Plotz, 1939, Tarr *et al.*, 1933; Weiss and Robb, 1933), so that it must be concluded that pulmonary congestion exists at such times also, and apparently is not greatly increased during the attack itself. These findings throw doubt on the concept that cardiac asthma and pulmonary edema are caused by rapidly developing stasis in the lungs consequent to sudden weakening of the left ventricle The long arm-to-tongue or -face circulation time of cardiac asthma is used to help differentiate it from bronchial asthma, where the circulation time is normal or somewhat reduced.

Venous pressure. — Although a few authors describe the venous pressure as unchanged (Oppenheimer and Hitzig, 1936; Weiss and Robb, 1933) or only occasionally and slightly elevated (Weiss and Robb, 1933, Wood, 1936), a majority record the finding of elevated venous pressures during and immediately after the attack (Villaret *et al.*, 1923, Tornquist, 1932; Altschule, 1937; Perera and Berliner, 1943) Richards *et al.* (1942) studied the intra-auricular and venous pressures in animals with spontaneous or induced pulmonary edema and found that both pressures were elevated, but the latter was raised relatively less, so that the normal gradient between the two disappeared. The cause of the elevation of venous pressure in attacks in man is not established, but it appears that diminished cardiac output, resistance to the flow of blood through the edematous lungs and probably also changes in intrapleural pressure are responsible for the

peripheral venous engorgement. Actually the venous pressure may occasionally fall to very low levels in pulmonary edema; this may occur when the attack is complicated or terminated by the development of a state of shock (Altschule, 1937; Stead and Ebert, 1942).

Arterial pressure. — The arterial blood pressure may be unchanged, but is often elevated and occasionally depressed during the attack. Elevation of the blood pressure above its usual level may occur at the onset of the paroxysm even before dyspnea becomes marked or even apparent. This rise appears to be consequent to vasoconstriction due to sympathetic activity for, at such times, the patient appears pale and sweaty. A fall in arterial pressure of varying degree may occur in association with the development of a greater or lesser amount of shock (Stead and Ebert, 1942).

Respiratory dynamics. — Few data bearing on respiratory function in man during paroxysms of cardiac asthma or pulmonary edema have been reported. Respirations visibly increase in rate and become labored. The vital capacity, low between attacks (Weiss and Robb, 1933), becomes lower during paroxysms (Weiss and Robb, 1933; Perera and Berliner, 1943) This observation implies not only encroachment upon space available for respiration but also an increase in rigidity and loss of elasticity of the lungs, as more fluid accumulates in the interstitial tissues. Both of these phenomena give rise to dyspnea, but the change in rigidity may also activate the Hering-Breuer reflex and lead thereby to hyperpnea. Another consequence of impaired pulmonary elasticity is a rise in intrapleural pressure, which should be associated with a corresponding rise in venous pressure. Other subdivisions of the lung volume may show changes resembling those seen in chronic congestive failure (Weiss and Robb, 1933).

Blood gases, tissue gases — The arterial blood oxygen saturation falls during attacks (Weiss and Robb, 1933), often to very low levels, as a consequence of the above-described changes in the lungs. This arterial anoxia causes the cyanosis and contributes to the dyspnea seen in the syndrome. In addition, it aggravates the severity of the edema of the lungs itself (Gesell, 1928; Maurer, 1940; M. F. Warren *et al.*, 1942*a*, *b*). The arterial carbon dioxide content may be normal or increased (Porges *et al.*, 1913) Carbon dioxide is much more readily diffusible than oxygen and, accordingly, the hyperventilation

that occurs during attacks should be enough to prevent the accumulation of carbon dioxide in any but very severe degrees of pulmonary edema. A single undetailed observation of the tissue gas tensions during an attack of pulmonary edema has been recorded by Sibree (1941*b*); increased tissue carbon dioxide tension and a normal oxygen tension are described. The accuracy of the latter observation may be questioned because the time required for equilibration of oxygen between the blood and the bubble of air introduced under the skin is longer than that for carbon dioxide; as is well known, attacks of cardiac asthma are usually of relatively short duration.

Blood lactate. — Harris, Jones, and Aldred (1935) reported elevation of the blood lactate at rest in a patient with cardiac asthma. This implies a high degree of tissue anoxia, apparently the consequence of the above-described changes in arterial blood oxygen saturation and possibly also of a decreased cardiac output. As pointed out previously, high blood lactate concentrations accentuate dyspnea (page 169).

Nocturnal occurrence of attacks. — A few patients have attacks of nocturnal dyspnea because they are orthopneic and slip down in bed while asleep, others have them in association with Cheyne-Stokes respiration, occurring spontaneously during sleep, or caused or exaggerated by sedatives that depress respiration. In most instances, the cause of the greater frequency of attacks of true cardiac asthma or pulmonary edema at night is not immediately apparent, this difficulty exists in large part because the cause of the paroxysms of pulmonary edema is not understood in general. Two phenomena appear to have some bearing on the problem: (i) respiratory depressants often cure and respiratory stimulants may enhance pulmonary edema and (ii) factors that increase inflow into or retard outflow from the lungs enhance while their opposites relieve pulmonary edema (Luisada, 1940). During sleep there is at first a spontaneous depression of respiration, which leads to an accumulation of carbon dioxide in the blood. In normal individuals this has no harmful effect, but in patients subject to attacks of pulmonary edema this excess of carbon dioxide may act as a respiratory stimulant and finally cause a paroxysm. Another phenomenon that also bears on the problem is the fact that when an individual is up and about for a time, the plasma volume is about 10 per cent less than when he is recumbent, appar-

ently because of a loss of fluid into the legs (page 229); this fluid returns to the circulation during the hours spent in bed, presumably as a result of a fall in venous pressure (Hooker, 1914). Accordingly, a patient with a tendency to pulmonary edema in effect receives an infusion of several hundred cubic centimeters of plasma when, after being up and about, he goes to bed. Convincing evidence in this direction, based on studies of vital capacity and plasma protein levels, has been published by Perera and Berliner (1943) and by Spealman *et al.* (1947). The observation of Harrison *et al.* (1934) that even bedridden patients exhibit a progressive fall in vital capacity and an increase in respiratory rate and minute volume toward evening is hard to explain; it has not been corroborated by other observers.

Shock during pulmonary edema. — The occurrence of a marked fall in arterial and venous blood pressure, rise in pulse rate and appearance of clinical manifestations of shock as a complication or terminal event in pulmonary edema is not rare. Although this phenomenon has not been studied completely, it is possible to make tentative suggestions as to its origin. Profound anoxia and marked sympathetic overactivity may occur during attacks; both favor the occurrence of shock. In addition, it must be borne in mind that edematous lungs may, judging by their weight, contain as much as a liter or more of plasma, blood or other fluid, which are thus removed from the general circulation. In this connection, it is of interest that hemoconcentration has been found to occur during attacks of pulmonary edema (Lemierre and Bernard, 1926; Stead and Ebert, 1942; Perera and Berliner, 1943). Further loss of circulating blood volume may result from venesection. Usually, however, the veins are collapsed and the venous pressure is low at this time, so that venesection is difficult or impossible. The importance of this factor may at times be demonstrable by means of the application of tourniquets; this may precipitate a fall in blood pressure, which may rise when the tourniquets are released The occurrence of profound and persistent shock together with pulmonary edema almost always results fatally.

Wheezing. — Asthmatic wheezing may be a consequence of heart disease. It is considered to be similar in origin to acute pulmonary edema; instead, however, of an outpouring of edema fluid into the alveoli with the production of crackling and bubbling râles, there

occurs spasm of the bronchi and the development of musical rhonchi. The bronchial spasm was shown to be reflex in origin by Weiss and Robb (1933); the origin of the reflex is obscure but it may be initiated by accumulation of interstitial edema fluid in the lungs. The differentiation of cardiac asthma from bronchial asthma is of great importance since morphia in large doses relieves the first and may cause death in the second; contrariwise, epinephrine relieves bronchial asthma and, in the doses used, may be fatal in cardiac asthma. If the differentiation cannot be made on clinical grounds, measurement of the circulation time is helpful (page 326). However, a severe paroxysm of wheezing may require immediate treatment before such measurements can be made; in such instances aminophylline, given intravenously, should be used since it controls both types of asthmatic paroxysm.

Effects of aminophylline. — The mechanism whereby aminophylline when given intravenously in doses of approximately 250 mg relieves bronchospasm is not established The drug is apparently a powerful relaxer of smooth muscle and this useful property results in relief of dyspnea and an increase in vital capacity in patients with cardiac asthma (Greene *et al.*, 1937, Heyer, 1946). However, the action of the drug also involves the smooth muscle of blood vessels and causes vasodilatation (Robertson and Faust, 1940) This phenomenon is useful in part because the resulting fall in venous pressure (Greene *et al*, 1937, Robertson and Faust, 1940; Steinberg and Jensen, 1946) causes a secondary decline in cerebrospinal fluid pressure (Greene *et al*, 1937, Robertson and Faust, 1940); a change of this sort may alleviate dyspnea (page 183). On the other hand, the vasodilatation that occurs also causes the capillaries to dilate and the arterioles to relax (Robertson and Faust, 1940). Starr *et al.* (1937) observed a decrease in peripheral resistance after the injection of theophylline. A consequent increase in cardiac output (page 200), and in the volume of peripheral blood flow (Stewart and Jack, 1940) is known to occur, and a reduction in circulation time has also been described (Steinberg and Jensen, 1946). Lowering of arterial pressure may act deleteriously on the heart in patients with coronary arteriosclerosis, and increased cardiac work may be dangerous in such individuals. Accordingly it is clear that aminophylline can be expected to cause cardiac pain or coronary failure in some patients

with sclerotic coronary arteries, and collapse in any individual susceptible to the effects of generalized vasodilatation. It is fortunate that the administration of the drug intravenously at a slow rate avoids most of the circulatory effects while preserving the bronchodilating action of aminophylline.

Effects of morphia. — It is widely held among clinicians that morphia, although not effective in every instance, is by far the most useful remedy for cardiac asthma and pulmonary edema The reason for its effectiveness is not known That it depresses the activity of the respiratory center, decreasing the respiratory minute volume (2, Dripps and Comroe, 1945) by decreasing respiratory rate, is established; changes in tidal air volume are variable. Harrison *et al* (1934) reported that morphia increased the vital capacity in cardiac patients, but other observers (Resnik *et al.*, 1935*a*, *b*) found no such change. The metabolic rate falls slightly after the administration of morphia (Resnik and Friedman, 1935*a*, Wangeman and Hawk, 1942) The arterial blood oxygen content may fall to a variable degree and the carbon dioxide content may rise slightly (Fraser, 1927, Wortis *et al.*, 1940); a fall in blood pH may also occur (Fraser, 1927). All of these slight but apparently deleterious changes in the blood may be associated with relief of dyspnea during an attack of pulmonary edema (Fraser, 1927). Changes in the cardiac output (Resnik *et al*, 1935*b*), the circulation time (Wortis *et al.*, 1940) and the cerebral blood flow (Wortis *et al.*, 1940) consequent to the action of morphia in therapeutic doses are not significant The effect of morphia on respiration is partly to relieve dyspnea but this phenomenon is not sufficiently marked to explain the striking benefit that is associated with its use. Its beneficial action may include the allaying of anxiety in some patients. It is possible, however, that its effectiveness in controlling pulmonary edema may be due largely to its depressing action on the respiratory center or on reflex arcs that are activated when pulmonary edema occurs (Luisada, 1940).

Effects of tourniquets. — The application of tourniquets at well above venous pressure has the obvious effect of impounding a considerable amount of blood in the extremities (Ebert and Stead, 1940), this is clearly visible in the veins and, to judge by the increase in capillary pressure that follows (Landis, 1930; Eichna and Bordley,

1939) it occurs in the capillaries also; the return of blood to the heart is therefore decreased. Measurements reveal decreased blood flow in limbs constricted by tourniquets (Friedland *et al*, 1941). This slowing of flow is only a temporary effect, lasting only as long as the tourniquets are in place. In addition, there is loss of fluid from the blood into the tissues of the limbs in which circulation is slowed (Ebert and Stead, 1940) Accordingly, there is an increase in plasma specific gravity or in plasma protein or hemoglobin concentration (3; Peters *et al.*, 1925, 1926), swelling of the limb occurs and lasts for a time after removal of the tourniquets (4; Landis *et al.*, 1932, 1933). The transudation of fluid is accompanied by a loss of chloride into the tissues, Dautrebande *et al* (1923) reported a loss of bicarbonate as well, but this has been denied by Peters *et al* (1926). The impounded blood shows an increase in carbon dioxide content and decrease in capacity (Dautrebande *et al*, 1923; Peters *et al.*, 1926) so that the pH falls The loss of fluid into the tissues is not, however, marked enough to raise the tissue pressure greatly (Burch and Sodeman, 1937).

The local rise in venous pressure and capillary pressure caused by the tourniquets is not the sole cause of this transudation of fluid and electrolyte, since it occurs even when the circulation to an extremity is cut off entirely (Dautrebande *et al*, 1923) Studies on the cutaneous capillaries in man have shown (5; Friedland *et al*, 1941) that tourniquets cause marked stasis and result in capillary dilatation, particularly in the venous limb, this increases the filtering surface It has also been shown that the application of tourniquets in normal man causes an elevation of tissue carbon dioxide tension (Sibree, 1941*a*) and a lowering of venous blood oxygen (Friedland *et al.*, 1941) and tissue oxygen tensions (Sibree, 1941*a*) The latter reduction might result in an increase in capillary permeability (page 155), although no increase in tissue fluid protein occurs until the tourniquet pressure reaches 80 mm-of-mercury (Landis *et al.*, 1932). It appears that the transudation of fluid into the tissues of the limbs is the consequence of the combined action of the elevated filtration pressure, increased filtering surface and possibly increased capillary permeability The result of the impounding of blood and loss of fluid in the extremities is a decrease in venous pressure in the unconstricted limbs. This has been described both in normal subjects and

in cardiac patients (von Tabora, 1910; Fuchs, 1921; Kountz *et al.*, 1942; McMichael and Sharpey-Shafer, 1944*a*; Warren and Stead, 1943); however, Brams and Golden report no fall in their patients (1935).

The right auricular pressure is also lowered (McMichael and Sharpey-Schafer, 1944*a*, *b*; Warren *et al.*, 1945). The lowered volume and pressure of the venous return flow results in an appreciable decrease in blood flow through the lungs, as observed by means of auricular catheterization in normal subjects by McMichael and Sharpey-Schafer (1944*a*); the left ventricular output must fall correspondingly. Roentgenographic studies by Kountz, Smith and Wright (1942) in dyspneic cardiac patients similarly indicate a fall in cardiac output. Warren *et al.* (1945), who also used auricular catheterization, observed no decrease in cardiac output. On the other hand, McMichael and Sharpey-Schafer (1944*b*), who found a decrease in the output of the heart when tourniquets were placed on normal subjects, found a slight rise in cardiac patients, an increase which is, however, not impressive. It is apparent that more work must be done in this field.

The application of tourniquets also results in a small rise in vital capacity or partially prevents the fall that occurs in the recumbent position (6; Asmussen *et al.*, 1939). The action of tourniquets is, therefore, to decrease the inflow into the lungs, thereby reducing the rate of edema formation and allowing the resorptive processes to catch up; this effect is prolonged somewhat by a transitory reduction of blood volume.

An interesting side effect of the application of tourniquets to all four extremities is a fall in skin temperature over these limbs and a rise in rectal temperature (Smirk, 1936; Steele, 1937); if the tourniquets are kept on for some time, the rise in rectal temperature may result in hyperpnea unless respiration is depressed with morphia.

Effects of positive pressure respiration — Positive pressure respiration is often helpful in controlling pulmonary edema. It acts apparently in a manner similar to tourniquets, but at a higher level, namely, the great veins in the thorax. Breathing against resistance raises the intrapleural pressure, thereby impeding flow through the great veins and into the lungs. It has been shown in man and dogs that increased intrapleural pressure raises the peripheral venous

pressure (7; Barach *et al.*, 1938, 1946). Studies in normal man show that positive pressure in the airway causes a fall in cardiac output (Richards, 1945; Otis *et al*, 1946*a*, *b*, Cournand *et al.*, 1948) and an increase in circulation time (Barach *et al.*, 1938, 1946); peripheral flow also decreases (Fenn and Chadwick, 1947). In the dog, slowing of peripheral blood flow has been found (Beecher *et al.*, 1943). Renal blood flow is apparently also decreased, for the urea clearance falls significantly (Drury *et al.*, 1947). Barach *et al.* (1938) found a fall in vital capacity in normal subjects breathing against positive pressure; a respiratory tracing reproduced by these authors (Barach *et al*, 1938) suggests also that the functional residual air is increased, as later measurements showed (Barach *et al.*, 1946). Rahn *et al.* (1946) also demonstrated an increase in functional residual air volume due to an increase in supplemental air, the complemental air decreased so that in their experiments the vital capacity was unchanged. Further studies (Barach *et al*, 1946, Rahn *et al.*, 1946) showed hyperventilation in normal subjects during at least part of the time when positive pressure was in force. No change in oxygen consumption occurred. The work of breathing was increased when pressures were elevated above any but the lowest levels.

According to Barach *et al.* (1938), cardiac patients show a somewhat greater rise in venous pressure and more increase in the circulation time than do normal subjects, but the vital capacity rises. A possible explanation for the rise in vital capacity is a reduction in the rigidity of the lungs found in congestive failure; this rigidity is due to an increased amount of blood in the lungs, a factor which would be counteracted by the impounding of blood in the periphery by positive pressure in the airway (Fenn *et al*, 1947) It is of interest that positive pressure respiration results in hemoconcentration (Barach *et al.*, 1946), this phenomenon is probably consequent to loss of fluid into the tissues and is comparable to the effect of tourniquets (page 225). However Henry *et al.* (1948) found no decrease in plasma volume.

Effects of venesection.—The removal of 300 cc or more of blood results in a fall in venous pressure in normal subjects and in cardiac patients (8; Loutit *et al.*, 1942; Stead and Ebert, 1942). The right auricular pressure also falls in normal subjects (Barcroft *et al.*, 1944;

McMichael and Sharpey-Schafer, 1944*a*; Warren *et al.*, 1945), as does the right ventricular pressure (Richards, 1945; Bloomfield *et al.*, 1946). These changes are accompanied by a considerable decrease in blood flow through the lungs in normal subjects (Barcroft *et al.*, 1944, McMichael and Sharpey-Schafer, 1944*a*; Richards, 1945), the left ventricular output must diminish correspondingly. The finding of Warren *et al.* (1945) that no fall in blood flow occurs in normal subjects is not in harmony with a large amount of data on cardiac physiology and cannot be accepted without substantiation. However, more recently Bloomfield *et al.* (1946) showed that venesection lowers the cardiac output in such patients The studies of Shenkin *et al.* (1944) by means of the ballistocardiograph, show decreases in cardiac output only with large venesections. On the other hand, little or no fall in cardiac output was found in cardiac patients by authors using older methods (Resnik *et al*, 1935*b*; McMichael, 1938), whatever decrease occurred apparently being a consequence of diminished oxygen consumption, since the arteriovenous oxygen difference did not change (Resnik *et al.*, 1935*b*). Similarly, studies made by auricular catheterization (Howarth *et al*, 1946, 1947, Sharpey-Schafer, 1946) show only inconsequential changes in cardiac output after venesection The circulation time is unchanged (Howarth *et al*, 1946).

Possibly the differences in the results are to be accounted for by the length of time that elapsed between the removal of blood and the making of the measurements; the abnormally large blood volume found in cardiac patients may also play a part. Any decrease in cardiac output that occurs is probably of short duration and is of no importance as a rule Venesection at times gives rise to vasoconstriction so that the arterial blood pressure is maintained; accordingly the peripheral resistance remains unchanged (Richards, 1945) or is increased (Barcroft *et al.*, 1944).

Studies by Barcroft *et al.* (1944) on the peripheral circulation after venesection are of interest in this regard. After removal of several hundred cubic centimeters of blood from a vein, the peripheral flow (Barcroft *et al.*, 1944), like the cardiac output, is diminished somewhat. However, if the subject faints, this reaction is associated with a sudden vasodilatation manifested by a fall in peripheral resistance and an increase in peripheral flow.

If the venous return does fall appreciably during venesection, the inflow into the lungs is diminished and edema thereby influenced favorably. The vital capacity in normal subjects (Glaser and McMichael, 1940) and in cardiac patients is increased by several hundred cubic centimeters (9; Platz, 1947). The precise nature of the change that occurs in the lungs after venesection is, however, difficult to state; Glaser and McMichael (1940) studied the subdivisions of the lung volume and found increases only in the complemental air and the measurements derived from it, namely, the vital capacity and total capacity. The respiratory minute volume (Resnik *et al*, 1935*a*, *b*) and with it the oxygen consumption falls in cardiac patients who have been bled. The changes in the lungs may occasionally result in an increase in arterial blood oxygen saturation (Grant, 1923) In addition, the hemodilution that follows venesection (Lemierre and Bernard, 1926; Ebert, Stead and Gibson, 1941) may in cardiac patients occur at the expense of the edema fluid. Following venesection the blood volume is restored to its previous level within twenty-four hours in normal subjects (Ebert, Stead and Gibson, 1941) and possibly more rapidly in decompensated cardiac patients The cerebrospinal fluid pressure falls after venesection (Roberston and Fetter, 1935), a factor that may ameliorate dyspnea (page 183) It should be borne in mind that all of these favorable actions on the lungs and possibly also on the brain must be balanced against the possibility, not very strong but not to be ignored, that venesection may precipitate shock in a patient with pulmonary edema by too great a lowering cardiac output and consequent sudden vasodilatation.

Effects of still-standing and sitting with feet dependent. — The venous pressure in the legs is higher during still-standing than during walking (page 36), consequently, the tendency toward filtration of fluid from the blood is increased in the former Still-standing results in hemoconcentration and a decrease in blood volume in normal subjects (Thompson *et al*, 1928; Waterfield, 1931, Youmans *et al.*, 1934; Asmussen *et al*, 1940) and presumably in cardiac patients also. It is probable that sitting with the feet hanging has the same effect, the available data bearing on this point (de Flora and Ciravegna, 1931) are not acceptable Many of the effects of a small or moderate venesection are apparently reproduced by still-standing

or sitting with feet dependent and, therefore, it is understandable why these procedures may give more relief in severe acute cardiac dyspnea than that afforded merely by sitting up in bed.

The view held by some clinicians that still-standing, or sitting or reclining with legs dependent, draws edema fluid into the legs from the lungs is based on unphysiologic reasoning. While gravity undoubtedly influences to a greater or lesser degree the distribution of edema fluid in a given organ or tissue, it is highly improbable that it will deflect it from one to another.

Effects of oxygen. — The administration of oxygen serves the obvious purpose of remedying the generalized anoxia that results from pulmonary edema (page 220). A further beneficial effect of oxygen therapy in pulmonary edema is that it tends to diminish the edema itself, for it has been shown (page 156) that anoxia increases the amount of transudation from the blood vessels of the lungs.

Summary. — Physiologic data bearing on acute pulmonary edema and cardiac asthma are not sufficiently complete to permit of generalizations as to the nature of these disorders. This unsatisfactory state is to some extent unavoidable, for attacks of pulmonary edema are relatively short in duration, frequently complicated by other disorders such as chronic congestive failure, arrhythmias or myocardial infarction, and often so severe as to make it impossible for patients to coöperate in studies. In addition, there exists a marked dichotomy of thought between clinicians, who study patients, and physiologists, who study mechanisms. The first named usually designate the condition by a physiologic term, namely, "left ventricular failure," which physiologists consider unacceptable The physiologists, on the other hand, adhere to a simple clinical designation, namely, "acute pulmonary edema," realizing that their studies of mechanism in man are fragmentary.

It would be helpful if clinicians would cease to think in terms of erroneous physiologic concepts. A large amount of physiologic work supports the theory that acute pulmonary edema and cardiac asthma are neurogenic and probably reflex in origin; clinical data do not show the contrary. Pulmonary edema is poorly understood, but whatever the final causative mechanisms may prove to be, it is established (i) that morphia, a drug which, in the doses used, apparently acts on nervous tissue, terminates most attacks; (ii) that the anoxia

which develops during attacks is ameliorated by oxygen; (iii) that factors which diminish inflow into the lungs also decrease total blood flow for a time and accordingly, the use of these mechanisms, namely, tourniquets, venesection and positive pressure respiration, is not entirely without hazard; and (iv) that the element of bronchospasm which is present is helped by aminophylline.

There is nothing to prevent the development of attacks of acute pulmonary edema in patients with chronic congestive failure. Indeed, it is not uncommon to see the two together, the paroxysmal syndrome developing as the chronic disorder worsens and disappearing as the chronic failure improves. It is clear that, under these circumstances, the treatment of the two syndromes is identical. However, the treatment of individual attacks of pulmonary edema, whether isolated or in association with chronic myocardial insufficiency, is that outlined above.

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Chapter II

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III

ANGINA PECTORIS
MYOCARDIAL INFARCTION

1. *Angina Pectoris*

Most physicians feel that the fundamental cause of angina pectoris is, largely or entirely, disease of the coronary arteries; accordingly, many studies have been made of the function of the coronary arteries and myocardium in patients with angina pectoris There are, therefore, few physiologic data on the status of the circulation as a whole in this syndrome.

Cardiac output —The minute volume output of the heart has been reported normal between attacks in patients with angina pectoris (Starr and Gamble, 1935; Bazett *et al.*, 1941, Altschule, 1944). In 1935, Starr and Gamble (1935), summarizing their studies with the ethyl iodide method, stated that the cardiac output was normal in patients with angina pectoris. Later, however, Starr and Wood (1943), using the ballistocardiograph to estimate cardiac output, found normal values in only five patients with angina pectoris and low values in nineteen, including fifteen whose cardiac output was 30 to 60 per cent below normal. Four of the latter group developed congestive failure while under observation, but no such complicating factor was present in the others Accordingly, other explanations must be invoked to explain the markedly subnormal cardiac output in these patients

One criticism of studies of the minute volume output of the heart made by means of the ballistocardiograph is that they afford no information on the relation of the volume of the cardiac output to

the metabolic requirements of the body. The importance of considering this relation in studies of the circulation in disease has already been emphasized (page 6). It is clear, therefore, that the value of data on cardiac output is impaired by the absence of corresponding data on metabolism, this is especially true in patients with angina pectoris, since many of them have low metabolic rates (Riseman and Brown, 1937; Altschule, 1944). The weight of the evidence appears to favor the conclusion that the general circulation is normal in relation to metabolic requirements at rest and in the absence of anginal pain in patients with angina pectoris. During attacks of angina pectoris in two patients, the cardiac output was found by Starr *et al.* (1938) to be elevated; the attacks were precipitated by emotion in one instance and by the injection of epinephrine in the other.

Circulation time.—Normal circulation time is reported in most instances of angina pectoris (Winternitz *et al.*, 1931; Bernstein and Simkins, 1939; Wood, 1936, Altschule, 1944), though Winternitz *et al* (1931) and Bain (1934) found it to be increased often; most of Bain's patients had evidence of congestive failure also. A recent analysis (Altschule, 1944) showed that increase of the circulation time in the absence of frank decompensation in angina pectoris was usually consequent to noncardiac factors.

Venous pressure.—The venous pressure is normal in patients with angina pectoris (Wood, 1936, Altschule, 1944).

Arterial pressure.—Approximately 50 per cent of patients are mild hypertensives (Riseman and Brown, 1937; Altschule, 1944).

Vital capacity.—The vital capacity is often somewhat low in patients with angina pectoris (Altschule, 1944) apparently as a consequence of such noncardiac factors as emphysema and obesity.

Occurrence of pain.—The circulation between attacks is normal in patients with angina pectoris, except for a high incidence of hypertension In everyday life, attacks of angina pectoris commonly occur at times when the cardiac output is increased, that is, during exertion or emotional upsets, or after heavy meals. The increased cardiac output reported by Starr *et al* (1938) during attacks of angina was caused by the factor precipitating the attack, rather than the attack itself; the precipitating factor was emotion in one case and the injection of epinephrine in the other. Both the former

(Grollman, 1929; Stead *et al.*, 1945) and the latter (Field and Bock, 1924; von Euler and Liljestrand, 1927; Starr *et al.*, 1937; Altschule and Iglauer, 1940; McMichael and Sharpey-Schaefer, 1944) have been shown to increase cardiac output. It is not valid, however, to conclude that attacks of angina pectoris are in every instance associated with increased cardiac output. For instance, sympathomimetic amines such as paredrine, which elevate blood pressure but do not increase cardiac output (Altschule and Iglauer, 1940), may cause anginal pain in patients with history of angina pectoris. A clinical counterpart of this phenomenon is angina pectoris associated with sudden hypertension (Lewis, 1931). It is clear from the formula * of Evans and Matsuoka (1915), $W = OP + \frac{1}{2}\ (w/g)V^2$, that an increase either in cardiac output or in blood pressure increases the work of the heart and, accordingly, it may be concluded that the occurrence of angina pectoris is usually related to increased cardiac work On the other hand, angina may occur when the work of the heart is decreased, that is, in cardiac arrhythmias with marked tachycardia (page 251) The factor responsible for angina in such situations appears to be myocardial anoxia consequent to inadequate flow through the coronary tree, a result of shortening of diastole.

The precise mechanisms underlying the production of pain by myocardial ischemia is unknown. Lewis(1935) showed that exercising a muscle under conditions of ischemia causes pain, an observation amply confirmed by others; however, there is no precise information indicating whether oxygen lack, carbon dioxide excesss, or the excessive production of some other metabolite is the direct cause of the discomfort At any rate it has been shown that the nerve fibers that carry coronary arterial pain run in the adventitia of these arteries (Katz *et al*, 1935). They are carried in the middle and inferior cardiac nerves and the thoracic cardiac rami to the middle and inferior cervical and the first four thoracic posterior roots (White and Smithwick, 1941). These axones are small, poorly myelinated or unmyelinated, and their rate of conduction is slow (Heinbecker and Bishop, 1935); they therefore resemble sympathetic motor neurones except that they run to the cord as a simple fiber without

* In this formula, W is the work done by the heart, O is the output of the heart, P is the mean blood pressure, w is the weight of blood, V is the velocity of the blood flow, and g is the acceleration due to gravity.

any synapse in the ganglion between a pre- and postganglionic fiber. Other components of the pain of coronary disease, such as pain in the neck or jaw, are apparently carried in the vagus nerve (White and Smithwick, 1941). The fact that most of the pain-carrying fibers enter the cord in the first four or five thoracic segments accounts for the typical referred pain over the skin of the shoulder, arm, or inner fingers

Anginal pain may be precipitated in patients with coronary sclerosis by induced anoxia. This phenomenon appears to be the consequence of (i) myocardial anoxia, and (ii) increased cardiac output and work due to lowered arterial blood oxygen saturation (page 70). It should be noted that one change induced by the inhalation of air containing low percentages of oxygen, namely, the fall in arterial blood oxygen level, is unpredictable (Graybiel *et al*, 1937, Houston, 1946). Consequently, changes in cardiac work and in vasomotor function are also variable. The use of anoxia in tests of the state of the coronary arteries has accordingly been criticized (Graybiel *et al.*, 1937, Houston, 1946).

A valid generalization based on physiologic data is a reaffirmation of the clinical concept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia. These considerations do not explain status anginosus, or recurrent angina at rest. Local spastic changes in the coronary arteries also appear to be important in the genesis of angina That diseased arteries frequently show vasospastic phenomena is well known to students of peripheral artery disease; there is no reason to doubt that coronary arteries may react similarly. Indeed, Freedberg *et al.* (1944) have shown that reflexes from the skin control the occurrence of anginal pain to a large degree, apparently by influencing the caliber of the coronary vessels. Similarly, there is evidence that distension of abdominal viscera may cause reflex coronary vasoconstriction (von Bergmann, 1932; Gilbert *et al.*, 1940). In addition, the relief of pain experienced by some patients after taking vasodilator drugs, such as nitrites, in doses too small to affect the general circulatory dynamics, is further evidence for the importance of coronary spasm in the causation of anginal pain. The fundamental defect in angina pectoris is, therefore, a decreased coronary circulation which, though adequate for the work of the heart

when the patient is at rest, becomes inadequate when coronary filling is somewhat impaired by spasm or other factors, or when the cardiac work is increased.

It is of interest that many patients with the anginal syndrome hyperventilate during the occurrence of pain but do not experience dyspnea (Boyer and Bailey, 1943); this phenomenon suggests that dyspnea need not be perceived when hyperventilation is present if more severe discomfort of other types occurs.

2. *Myocardial Infarction*

Circulatory dynamics. — Data describing the circulation in patients following myocardial infarction are scanty. A few measurements of cardiac output by unreliable methods suggest that lowering of the output of the heart probably occurs (Grishman and Master, 1941; Starr and Wood, 1943). The finding of decreased blood flow through the fingers recorded by Mendlowitz (1942) is difficult to interpret with certainty since the circulation in the hands is strongly influenced by neurogenic factors and may not indicate the state of the circulation as a whole. The circulation time is normal or increased (Bain, 1934; Fishberg *et al*, 1934; Neurath, 1937; Selzer, 1945; Stead and Ebert, 1942); the venous pressure may be normal, low or elevated (Fishberg *et al*, 1934; Griffith *et al*, 1934; Stead and Ebert, 1942; Selzer, 1945) Of special interest is the finding by all of these authors of low values for venous pressure in some instances, suggestive of a state of shock due to impaired peripheral vascular mechanisms. In this connection a single observation of temporary loss of tone in the small vessels recorded by Capps (1936) is particularly pertinent. The vital capacity is often diminished (Selzer, 1945). Fishberg, Hitzig and King (1934) found the blood volume markedly variable, but these authors used a method not now considered reliable. Stead and Ebert (1942) found the plasma volume slightly diminished and detected evidences of hemoconcentration, but all of their patients had some degree of pulmonary edema, which in itself may cause hemoconcentration (page 222); Cameron *et al* (1947) found the blood volume normal.

Interpretation of these findings is difficult. It is impossible to characterize the circulatory phenomena consequent to myocardial infarction *per se*, for it is probable that the cardiovascular changes that have been found are largely determined by the occurrence of associated conditions such as shock, pulmonary edema, congestive heart failure, and cardiac arrhythmias.

Shock —The shock that occurs during or after myocardial infarction is properly regarded as neurogenic by Fishberg *et al.* (1934); it is probably not due solely or largely to cardiac weakness, as Stead and Ebert suggest (1942) Whatever its mechanism, it is often self-limited and, when more persistent, may be benefited by infusions of plasma, even in the presence of pulmonary edema.

Pulmonary edema —This disorder is probably neurogenic in origin (page 218), for it occurs irrespective of whether the left or right ventricle is the seat of infarction Stead and Ebert (1942) pointed out that the circulation time may show surprisingly little increase in patients with pulmonary edema following myocardial infarction It is apparent that much work must be done in this field, the vast amount of theorizing that occupies space in the medical literature has little established validity.

Cardiac arrhythmias —The occurrence of ventricular arrhythmias, that is, extrasystoles or tachycardia, after myocardial infarction is probably consequent to the formation of hyperirritable foci in the damaged ventricular myocardium It is probable, however, that the other common arrhythmias in this disorder are vagal in origin It has been shown that atropine may abolish partial heart block after myocardial infarction (Master *et al*, 1938), available evidence also suggests that auricular fibrillation and flutter are due to vagal reflexes acting on the auricles (Klainer and Altschule, 1942, Altschule, 1945).

Autonomic function —Reference has already been made to the probable vagal origin of some cardiac arrhythmias after myocardial infarction, it is likely that pulmonary edema seen in this condition is also reflex The gastric distention and vomiting may also be vagal in origin Definite evidence of increased vagal tone is afforded by the development of hypersensitivity of the carotid sinus reflex after myocardial infarction (Sigler, 1942).

The occurrence of bluish pallor, cold skin, and also a reduction in

peripheral blood flow (Mendlowitz, 1942), all suggest sympathetic stimulation. Additional evidence in this regard is the not uncommon finding of a level of arterial blood pressure above what is usual in a given patient early in the course of myocardial infarction.

Intermediary metabolism. — Data are available that suggest the occurrence of an "adaptation reaction" after myocardial infarction Creatinuria develops early (Herrmann and Decherd, 1934; Altschule and Rosenfeld, 1947), negative nitrogen balance and elevated blood amino acid levels soon become manifest also (Altschule and Rosenfeld, 1947). Similarly, disturbance of carbohydrate metabolism appears with elevation of the blood lactate and pyruvate levels (Davidson *et al*, 1946; Altschule and Rosenfeld, 1947); glycosuria and hyperglycemia are well known to occur, either *de novo* or as evidence of the making overt of latent diabetes mellitus.

Blood clotting — A tendency toward intravascular clot formation is common after myocardial infarction. Blood clotting has been found to be accelerated by some authors (de Takats, 1943; Hines and Kessler, 1945, Ogura *et al.*, 1946; Cameron *et al.*, 1947). The responsible mechanisms are unknown but may include the effects of bodily injury *per se*, increased viscosity of the blood due to dehydration or the loss of plasma into or through edematous lungs, and slowing of the blood flow consequent to shock, congestive failure, or oversedation.

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Chapter III

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IV

CARDIAC ARRHYTHMIAS

1. *Auricular Fibrillation. Action of Quinidine*

The effects of auricular fibrillation in man have been studied in most cases by observing the changes that follow the restoration of normal rhythm, either spontaneously or as a result of the administration of quinidine. The findings are colored by the fact that many of the patients so studied had, in addition to the arrhythmia, valvular heart disease or some degree of myocardial insufficiency, or both. Therefore, absolute uniformity in the findings is not to be expected.

Restoration of normal sinus rhythm is associated with a rise in cardiac output and a fall in arteriovenous oxygen difference in most instances (1; Stewart *et al.*, 1938), occasionally these evidences of improved cardiac function do not occur (Resnik *et al*, 1935; Stewart *et al.*, 1938; Smith *et al.*, 1930). The venous blood oxygen content usually rises (Stewart, 1923), this finding indicates an improvement in peripheral blood flow and increased oxygen tension in the tissues. Often, however, the improvement in cardiac function after reversion is not great enough to be considered significant, especially in instances where the ventricular rate was not rapid during fibrillation. Quinidine also has a vasodilator action (Ferrer *et al*, 1948). Changes in circulation time and venous pressure (Stewart *et al.*, 1938; Lequime, 1940), and in vital capacity (Stewart, 1923; Stewart *et al.*, 1938) are variable The respiratory minute volume may fall somewhat with a consequent rise in alveolar air carbon dioxide content (Smith *et al*, 1930); there is a simultaneous decrease in oxygen consumption (Stewart, 1923). The observations of Craw-

ford (1926) on the behavior of the cutaneous capillaries in patients with auricular fibrillation suggest that changes occur in the caliber of these vessels which are independent of the heart beat; the significance of this finding is not clear.

To summarize, auricular fibrillation causes a variable degree of reduction in cardiac output, with the expected secondary changes in circulation and respiration It may, therefore, precipitate congestive failure, or aggravate it if it is already present. In occasional instances the amount of impairment of cardiac function caused by the arrhythmia may be such as to exert a decisive role in determining the presence or absence of disability; it is not rare for patients with established heart disease and only mild discomfort to date the onset of severe symptoms from the hour of the development of auricular fibrillation. In other instances the only complaint may be palpitation. The common occurrence of auricular fibrillation in association with disease of the mitral valve is worthy of note (page 285)

2. *Auricular Flutter*

The circulation and respiration in auricular flutter have not been studied extensively. Although the mechanism of flutter closely resembles that of auricular fibrillation, the cardiovascular dynamics and symptoms are more nearly similar to those of the tachycardias, discussed in the following sections, because of the usual occurrence of a persistently rapid ventricular rate. Auricular flutter causes a fall in cardiac output with increase in arteriovenous oxygen difference and in circulation time, elevation of venous pressure and decrease in vital capacity (Lequime, 1940, Stewart *et al*, 1938).

3. *Auricular Tachycardia*

Although at times the only discomfort associated with auricular tachycardia is palpitation, this arrhythmia often gives rise to more disabling complaints Auricular tachycardia is of particular interest because it often affects the normal heart, and causes changes in the

circulatory dynamics that resemble in varying degrees of severity those of chronic congestive failure. In some patients, however, the clinical manifestations and physiologic changes are those of collapse, while in still other instances cardiac pain may be the chief complaint

Cardiac output. — All authors agree that a considerable decrease in cardiac output and increase in arteriovenous oxygen difference occur during paroxysms of auricular tachycardia (2; Stewart *et al.*, 1938). The lowered minute volume output appears to be partly due to marked shortening of diastole, so that inadequate filling of the heart occurs. Myocardial weakness may also occur as a consequence of shortened diastole, since recovery of the heart muscle after each beat may be incomplete and the coronary flow, maximal during diastole, is probably decreased; the fall in cardiac output varies roughly with the rise in rate above 150. In addition, a fall in blood pressure (see below) may further diminish the coronary flow. The output of the heart per beat is decreased considerably more than the output per minute because of the marked tachycardia; the output per beat may be decreased to one quarter or one fifth of the normal.

Circulation time. — The arm-to-tongue time is long (Winternitz *et al.*, 1931; Lequime, 1940, Stewart *et al.*, 1938). Neurath (1937) stated that it might be either short or long in paroxysmal tachycardia; he may have included patients with sinus tachycardia

Venous pressure. — Venous engorgement is of frequent occurrence during paroxysms of auricular tachycardia and the venous pressure has been reported as elevated (Hooker and Eyster, 1908; Lequime, 1940; Stewart *et al.*, 1938); Tornquist (1932), however, found it to be normal.

Arterial pressure — A profound fall in blood pressure with narrowing of the pulse pressure is not uncommon during paroxysms of this arrhythmia. Considerable decreases in blood pressure are often associated with collapse.

Vital capacity. — Decreases in vital capacity are the rule (McClure and Peabody, 1917; Carter and Stewart, 1923); however, they do not always occur (Stewart *et al.*, 1938). The occurrence of a lowered vital capacity indicates that an appreciable degree of pulmonary vascular engorgement may occur during paroxysm.

Blood gases. — The arterial blood oxygen saturation may be normal (Barcroft *et al.*, 1921; Meakins, 1922) or low (Carter and

Stewart, 1923), depending presumably on the degree of pulmonary stasis that occurs. The venous blood oxygen content is uniformly markedly lowered (Barcroft *et al.*, 1921; Carter and Stewart, 1923), as is to be expected from the decrease in cardiac output. The low venous oxygen content implies peripheral stagnation and low tissue oxygen tensions. The carbon dioxide content of the arterial blood is low as a consequence of dyspnea, whereas that of the venous blood is normal under these conditions because of stasis (Carter and Stewart, 1923).

Congestive failure — The cardiovascular dynamics of this arrhythmia are similar to those of chronic cardiac decompensation in that the cardiac output is low, the arteriovenous oxygen difference is increased, the circulation time is increased, venous blood oxygen content is decreased, arterial blood carbon dioxide content is lowered, venous pressure is elevated, and evidences of pulmonary congestion are present in the form of diminished vital capacity and, at times, lowering of arterial blood oxygen saturation Dyspnea, orthopnea, cyanosis and gastro-intestinal disturbances are, therefore, to be expected where the circulatory changes consequent to arrhythmia are severe enough, or where they occur in a milder degree in a patient with a previously damaged heart The fact that edema in visible amounts does not occur is probably consequent to the short duration of most paroxysms; some increase in extracellular fluid may occur but it is not enough to become apparent on clinical examination.

The cardiovascular physiology of auricular tachycardia shows two important differences, probably related, from those of chronic cardiac decompensation One is the common occurrence of significant and often marked decreases in arterial blood pressure. Starr and Rawson (1940), basing their conclusions on observations made upon a mechanical model of the circulation, emphasized the fact that when cardiac output falls, the arterial pressure will do likewise unless either vasoconstriction or an increase in blood volume occurs. In some patients pallor and a cold, sweaty skin suggest the occurrence of vasoconstriction due to sympathetic activity This phenomenon probably accounts for maintenance of the arterial blood pressures at or near normal levels in many instances In other patients, however, vasoconstriction is inadequate and the blood pressure falls. It is unlikely that an increase in blood volume occurs during paroxysms of auri-

cular tachycardia; the common occurrence of sudden hypotension suggests that this is so and, besides, the attacks are usually too short in duration to allow appreciable new formation of blood. The fact that elevation of venous pressure, occasionally in a striking degree, can occur without increase in blood volume is evidence against the concept (page 35) that the latter is the sole or most important factor in the venous hypotension of chronic cardiac decompensation; the importance of back pressure from the failing heart seems to be established

Collapse. — The low cardiac output, increased arteriovenous oxygen difference, low venous blood oxygen content and profound hypotension, together with clinical signs of collapse, emphasize the similarity between the dynamics of auricular tachycardia and those of shock. The development of the complete picture of shock, with suppression of cellular oxidations and fall in oxygen consumption, does not appear to occur in the collapse associated with arrhythmias, the decreased oxygen consumption described by Barcroft *et al.* (1921) in their patient was associated with a fall in respiratory minute volume, and may have been due to technical error or to the effects of large amounts of sedation given during the paroxysm. An important difference between the changes of surgical shock and those of collapse due to arrhythmia is the maintenance of venous pressure at high levels in auricular tachycardia. This rules out reduced venous return consequent to impaired peripheral vascular function as the cause of the collapse seen in this syndrome and shows that its origin is primarily cardiac. It would seem that the collapse associated with the arrhythmia would not be benefited by infusions.

Chest pain. — The occurrence of anginal pain in auricular tachycardia is not uncommon Decreased coronary flow, caused either by a profound fall in blood pressure or by marked shortening of diastole, or both, is presumably the cause, for cardiac work is not increased but actually may be considerably diminished.

4. *Ventricular Tachycardia*

The circulatory and respiratory physiology of paroxysmal ventricular tachycardia is much like that of auricular tachycardia The former arrhythmia, however, usually occurs in patients who have serious preëxisting heart disease, so that the change in cardiac rhythm as a rule is associated with very serious symptoms

Circulation — Marked decreases in cardiac minute volume output and increases in arteriovenous oxygen difference occur as a consequence of ventricular tachycardia (Dieuaide, 1924, Dogliotti *et al.*, 1937*b*; Stewart *et al*, 1938). The arm-to-tongue time is increased, often markedly, and elevation of venous pressure is the rule during the paroxysm (Dogliotti *et al*, 1937*b*; Stewart *et al*, 1938). The capillaries show changes similar to those of congestive failure (Dogliotti *et al*, 1937*b*) and the resting blood lactate level has been reported elevated in one patient (Hallock, 1939). The blood pressure usually falls, often to low levels

Respiration. — The vital capacity is diminished during paroxysms of the arrhythmia (Stewart *et al*, 1938). Respiratory rate and minute volume rise, with a consequent fall in alveolar carbon dioxide content (Dieuaide, 1924); there is also an increase in oxygen consumption (Dieuaide, 1924; Stewart *et al.*, 1938).

Blood gases. — The changes in the concentrations of the various blood gases are in accord with the observed changes in circulation and respiration The pulmonary congestion that occurs gives rise to a fall in arterial blood oxygen saturation and the marked slowing of the circulation present causes an additional decrease in venous oxygen content (Dieuaide, 1924) A fall in alveolar carbon dioxide content occurs and is paralleled by a decrease in arterial blood carbon dioxide content, in the one case reported, to a marked degree (Dieuaide, 1924), so great was the dyspnea in this patient that enough carbon dioxide was washed out of the arterial blood to leave him with a slightly lowered venous carbon dioxide content also, in spite of the slowed circulation and increased oxygen consumption.

Symptoms. — As in the case of auricular tachycardia, ventricular tachycardia may manifest itself by dyspnea of varying degree, cardiac pain, or collapse. The relatively more common occurrence of

ventricular tachycardia in association with serious heart disease, such as myocardial infarction, tends to make the picture of shock or of severe dyspnea more striking.

5. *Nodal Tachycardia*

The reported data (Stewart *et al.*, 1938) record a slight fall in cardiac output with no change in venous pressure in a patient with this arrhythmia.

6. *Complete Heart Block*

Although a number of studies of the general circulatory changes in patients with complete block have been published, uniformity in the findings is lacking. This is perhaps to be accounted for by the fact that heart block usually occurs as a complication of coronary artery disease, and the patients often manifest myocardial insufficiency in addition to the arrhythmia; indeed, in many instances, chronic congestive failure dominates the picture, the arrhythmia being only incidental.

Cardiac output. — The output of the heart per minute is reported as normal by most observers (3; Stewart *et al.*, 1938), while some record low values (4). Some of the patients described by the latter authors had gross congestive failure. The low values reported by Starr *et al.* (1934) and Stewart *et al.* (1938) were associated with low metabolic rates, so that the cardiac output was normal in relation to oxygen consumption. The stroke volume is of course very large, since the pulse rate is low.

Circulation time. — The arm-to-tongue or -face time has been described as normal or increased (5; Ellis and Weiss, 1931; Stewart *et al.*, 1938). Similarly, the ether time may be normal or long (Hitzig, 1935).

Venous pressure. — Normal values of venous pressure are described in all reported cases (Dogliotti *et al.*, 1937*a*; Ellis and Weiss, 1931; Hitzig, 1935; Stewart *et al.*, 1938).

Arterial pressure. — The arterial blood pressure characteristically is markedly elevated in systole, usually to or above 200 mm-of-mercury, while the diastolic level is normal or only slightly elevated. The wide pulse pressure is probably to be accounted for by the very much increased output of blood with each heart beat.

Capillaries. — A single observation records dilatation and slow flow in the capillaries of the nailfold (Dogliotti *et al*, 1937*a*); this may not be typical as the patient so studied also had a long circulation time.

Respiratory dynamics. — A single report records somewhat decreased values for vital capacity (Ellis and Weiss, 1931); in this age group the low values need not be due to pulmonary congestion, but may be associated with emphysema. The respiratory minute volume is usually normal, but may be somewhat increased when the cardiac output is lowered (Smith *et al.*, 1930), in the latter case, the alveolar carbon dioxide content is diminished; otherwise it is normal (Ringer and Altschule, 1930). The arterial blood oxygen saturation is normal in uncomplicated cases (Ellis and Weiss, 1931).

Effect of exercise and fever. — Alt *et al* (1930) found a normal or almost normal increase in cardiac output when their patients did light exercise Menne and Lauter (1931) and Stollreiter (1947) recorded an abnormally small increase Ellis and Weiss (1931) found a normal femoral arteriovenous oxygen difference and a normal blood lactate curve in their patients after moderate exercise. The increase in pulse rate during fever is small in patients with heart block (Gilchrist, 1934).

Symptoms. — Although some of the physiologic studies record normal responses in patients with heart block during light or moderate exercise, it is not unlikely that in severe exertion the cardiac output may fail to increase normally; the possible rise in pulse rate is small, and the increase in stroke volume must be limited because the output per beat is almost maximal with the patient at rest. Accordingly, patients with heart block may during exertion exhibit dyspnea or weakness which, strictly speaking, are not evidences of myocardial insufficiency. Such patients show little benefit after digitalization. On the other hand, patients who already have valvular heart disease or some degree of myocardial disease may develop full-blown congestive failure with the onset of complete heart block. Such patients,

their stroke output limited by disease, are able to maintain their circulations at approximately a normal level by means of an increased pulse rate, but when complete heart block supervenes the cardiac output falls and the manifestations of cardiac decompensation appear. These patients may benefit from digitalization by virtue of the fact that the drug gives rise to an increase in output per beat through increased force of contraction.

The problems involved in the various types of syncopal attack are many. Often these attacks are precipitated by a change from partial to complete block; presumably a marked fall in cardiac output occurs in such instances. In other cases, the syncopal attacks may develop even though complete block has been established for some time. Ventricular standstill or fibrillation may account for some of these, but others seem to be related to exercise or the ingestion of a particularly large meal Presumably here a limited ability to increase cardiac output, together with increased demand for blood flow to the muscles or viscera, results in a decrease in cerebral blood flow.

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Chapter IV

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V

PERICARDITIS

Although many observers have noted abnormal elevation of the venous pressure at rest or after exercise (1), and also increased spinal fluid pressure (Porot, 1930) in pericarditis in general, it is more illuminating in discussing the cardiovascular dynamics of pericarditis to divide it into (i) that due to fibrous pericarditis or concretio cordis and (ii) that due to acute or subacute pericarditis with effusion.

1. *Concretio Cordis*

In concretio cordis the heart is encased in a tough shell which prevents dilation in diastole and may also, by virtue of fibrous bands, constrict the great veins as they enter the heart.

Cardiac output. — All authors report low values of cardiac output, associated with an increased arteriovenous oxygen difference (2; Burwell *et al*, 1932, 1935, 1938; Stewart *et al*, 1938*b*), in some instances, however, the decreases in minute volume output are not great, and one author found normal values in his case (Debler, 1937). Since the heart is usually not enlarged greatly, if at all, the output per minute in relation to size is not decreased as much as in chronic congestive failure, where cardiac enlargement is the rule. Following exercise an abnormally small increase in cardiac output has also been recorded (Burwell and Strayhorn, 1932); similarly, no increase in the output of the heart occurred in one case after a large rapid intravenous infusion (Lyons and Burwell, 1946). The cause of the decreased minute volume output of the heart is not myocardial weak-

ness, for after successful removal of the constricting shell or of fibrous bands, the cardiac output is usually restored to or toward normal.

Peripheral blood flow. — A single observation records the finding of peripheral blood flow in the normal range (Stewart *et al.*, 1946). No increase occurred after digitalization, in contradistinction to chronic congestive failure, where a considerable increase occurred.

Circulation time. — The arm-to-tongue time is long (3; Stewart *et al.*, 1938*b*). An interesting observation is that the ether time is usually normal (Stewart *et al*, 1938*b*, 1939*a*, *b*); either most of the retardation of blood flow apparently occurs in the lungs or the ether time is not a significant measure.

Venous pressure. — All authors report elevated values, usually between 20 and 40 cm-of-water, for venous pressure in concretio cordis (4; Burwell *et al.*, 1932, 1935, 1938, Stewart *et al*, 1938*b*), this includes the femoral venous pressure (Burwell and Flickinger, 1935). An excessive rise during exertion or intravenous infusions has been noted (Burwell and Blalock, 1938; Lyons and Burwell, 1946). Increased salt intake also increased the venous pressure somewhat in one instance (Lyons and Burwell, 1946). After successful operation the venous pressure returns to or toward normal An interesting phenomenon which should be further investigated is that described by Veal and Hussey (1940), these authors reported that rapidly repeated squeezing of a rubber bulb — too little exertion to raise the venous pressure in myocardial insufficiency — will elevate it greatly in the exercising limb if there exists an obstruction to venous flow such as that caused by pericarditis or superior vena caval occlusion. If corroborated, this may afford a helpful diagnostic test to assist in differentiating between chronic congestive failure and pericardial disease.

Right auricular and right ventricular pressures. — The right intra-auricular pressure is elevated and the normal gradient between the venous and right auricular pressures is absent (Richards *et al*, 1941, 1942; Bloomfield *et al*, 1946), this finding suggests that outflow from the lungs is also obstructed. The elevated right ventricular pressure that has been noted (Bloomfield *et al*, 1946) has the same significance.

Arterial pressure. — A low arterial blood pressure with small pulse pressure is characteristic of the syndrome, and pulsus para-

doxicus occurs in most instances also. The arterial blood pressure and pulse pressure often return to normal after operation, but many exceptions to this finding occur.

Vital capacity. — The vital capacity is often low, usually rising after operation (Beck and Cushing, 1934; Beck and Griswold, 1930; *Burwell and Strayhorn, 1932;* Lyons and Burwell, 1946); other authors found that a postoperative increase did not occur in every instance (Heuer and Stewart, 1939; Stewart *et al.*, 1938*b*, 1939*a*, *b*). Possibly the effects of an extensive intrathoracic operation are sufficient to mask the increase in vital capacity which might otherwise occur. The decreased vital capacity, together with the above-described changes in right intra-auricular pressure, indicate that some degree of stasis exists in the lungs in concretio cordis.

Blood volume. — The plasma volume, red cell volume and total circulating blood volume are increased (Burwell and Blalock, 1938; Lyons and Burwell, 1946; Smith and McKisack, 1902). This change is compensatory to the low cardiac output and resembles that seen in chronic cardiac decompensation, although it may be less marked.

Cerebrospinal fluid pressure. — The spinal fluid pressure is elevated, as is to be expected in the presence of increased venous pressure (Burwell and Blalock, 1938). Nevertheless, signs of increased intracranial pressure do not occur.

Hepatic function — Icterus is not uncommon in concretio cordis and elevations of the plasma bilirubin and dye retention have been recorded (Ottenberg *et al.*, 1924). The early development of severe liver damage in this syndrome is well known and appears to be associated with very high venous pressure, for it also occurs in patients with severe disease of the tricuspid valve.

Blood carbonic anhydrase. — A single observation records the finding of normal values of blood carbonic anhydrase in one patient (Lambie, 1938).

Symptoms — The occurrence of symptoms resembling those of congestive failure is not surprising. The low cardiac output, evidences of stasis in the lungs, high spinal fluid pressure, increased blood volume, venous engorgement, and increased venous blood deoxygenation readily explain dyspnea on exertion, edema, orthopnea and cyanosis, such as occur in this disorder On the other hand, dyspnea is usually not severe, edema of the ankles may be absent and orthopnea

is often mild or absent in patients with constrictive pericarditis, even though the cardiovascular dynamics in this condition resemble those of chronic congestive failure; in addition, the early development of ascites some time before the appearance of ankle edema is the rule.

Although the cardiac output is often quite low in concretio cordis, in some patients it is not greatly decreased. In most instances, the lungs do not become as markedly congested as in patients with chronic cardiac decompensation. The lessened degree of dyspnea enables the patients to be fairly active, so that the lowering of venous pressure which occurs with walking (page 36) and maintennce of normal tissue tension through good muscle tone may act to inhibit the development of peripheral edema; an additional factor is the persistently normal plasma protein level (Burwell and Blalock, 1938; Biorck *et al.*, 1948). Moreover, the early development of ascites (ascites precox) often makes the patient seek medical attention long before embarrassment of cardiac function becomes severe. Ascites precox is explained by the early development of severe hepatic disease where, as in other cardiac disorders, venous pressures are markedly elevated; a very high thoracic duct pressure associated with concretio cordis is also a factor (Blalock and Burwell, 1935). The common absence of severe orthopnea in spite of very high venous and spinal fluid pressures is puzzling; one explanation is the absence of severe pulmonary changes in most cases. Also, it is the author's impression that patients with very high cerebrospinal fluid pressures consequent to marked elevations of venous pressure usually have a good deal of clouding of the sensorium, so that they are likely to be less troubled by symptoms than are other individuals.

2. *Pericardial Effusion*

Cardiac output. — The output of the heart has been reported as diminished, with a return to or toward normal after paracentesis (McGuire *et al.*, 1937, Stewart *et al*, 1938*a*; Warren *et al.*, 1946). On the other hand, Ewig and Hinsberg (1931) found it normal in their case before and after pericardial tap. Fletcher (1945) also found no rise in the output of the heart after a pericardial tap in his

patient with pericarditis, but the patient was apparently moribund, for he died of pulmonary infarction within a few hours. In addition, LeBlanc (1922) found the arterial and venous blood gas contents to be normal in his case, implying a normal cardiac output also. It is understandable that variations might occur from case to case, depending upon the amount of pericardial fluid and the degree of tamponade.

Circulation time. — The arm-to-tongue time is usually reported as increased; it decreases after paracentesis (Duras, 1944; Esser and Berliner, 1943, Stewart *et al.*, 1938*a*; Neurath, 1937). McGuire et *al.* (1937) found the circulation time normal in their patient.

Venous pressure — The venous pressure is elevated and falls after paracentesis (Fletcher, 1945; McGuire *et al.*, 1937; Stewart *et al*, 1938*a*; Neurath, 1937); Stewart *et al* (1938*a*) demonstrated the close relation that exists between the intrapericardial pressure and the peripheral venous pressure during paracentesis in a patient with a pericardial effusion.

Right auricular pressure. — The pressure in the right auricle is high and also falls after paracentesis (Fletcher, 1945; Warren *et al.*, 1946).

Arterial pressure; peripheral resistance. — Depending upon the degree of tamponade, there is a variable reduction in the arterial blood pressure and pulse pressure. They usually, but not invariably, return to normal after pericardial tap (Stewart *et al.*, 1938*a*). The peripheral resistance is elevated before paracentesis (Warren *et al.*, 1946).

Vital capacity. — The vital capacity is low (McGuire *et al.*, 1937; Stewart *et al.*, 1938*a*, Neurath, 1937), either as a consequence of encroachment on the lungs by the distended pericardium, or because of pulmonary stasis secondary to compression of the pulmonary veins, or both.

Cutaneous capillaries. — Freedlander and Lenhart (1922) found in the cutaneous capillaries the changes described above for chronic cardiac decompensation (page 47).

Symptoms. — The prominent symptoms in patients with pericardial effusion are usually those of the traumatic or febrile manifestations of the disorder that causes it, and also the local pain or other discomfort. In addition, if the degree of tamponade is appre-

ciable, a state of shock develops and must be treated. This type of shock is of interest because of the venous engorgement that is part of the picture Here, as in the cardiac arrhythmias, the fall in cardiac output is usually too rapid to be compensated by an increase in blood volume, so that shock, rather than congestive failure, is the rule. When the effusion develops slowly, however, a syndrome resembling in many ways that of chronic congestive failure may result It must be remembered that when the heart is dilated or hypertrophied by antecedent disease, a relatively small pericardial effusion may cause symptoms out of proportion to its size, since there is a limit beyond which the pericardium will not stretch.

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VI

CONGENITAL AND ACQUIRED CARDIAC DEFECTS

Two developments, namely, catheterization of the right side of the heart and the application of surgery to the handling of patent ductus arteriosus, coarctation of the aorta and pulmonic stenosis, are making available data on the physiology of congenital heart disease formerly not obtainable It will be many years before all of these data will be secured; accordingly, the present discussion is essentially a review of the older literature and consideration of such of the newer material as is available.

1. *Patent Ductus Arteriosus*

The circulation in patients with patent ductus arteriosus is not distributed in a normal manner The output of the right ventricle is equal to the amount of blood brought to it and is, therefore, identical with the peripheral (systemic) flow. However, this volume of flow is not the same as that which passes through the lungs, since the latter consists of the output of the right ventricle, to which is added a portion of the flow from the left. The left ventricular output comprises the volume shunted through the lungs together with that sent to the periphery, the latter equaling the output of the right ventricle. In effect, therefore, the output of the left ventricle is equal to the volume of blood flow through the lungs

Cardiac output. — A few studies by older methods of measuring cardiac output have been recorded Lequime (1940) and Richards (1931) investigated by means of rebreathing methods the concentra-

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Arterial oxygen saturation. — This is normal since the shunt is from left to right (Eppinger *et al*, 1941; Dexter *et al.*, 1946*a*, *b*, 1947). As Dexter *et al.* (1946*a*, *b*, 1947) and Johnson *et al.* (1947) have shown, the pulmonary arterial blood contains more oxygen than does that of the right ventricle.

Blood volume. — Although the blood volume is within the normal range in patients with this disorder, a slight decrease occurs after ligation of the patent shunt (Eppinger *et al*, 1941; Nylin and Biörck, 1947).

Symptoms. — The manifestations of persistence of a patent ductus arteriosus depend in large measure upon the size of the fistula between the aorta and the pulmonary artery. This is true not only of the loudness and character of the murmurs but also of the other clinical features as well. Thus, with a large ductus, the peripheral signs of aortic insufficiency, namely, wide pulse pressure, Duroziez's sign, and capillary pulsation, may be present at rest; with smaller defects they may appear only after exercise or may even be absent entirely. Similarly, the diastolic murmur ordinarily heard at rest may, in occasional instances, appear only after exercise.

The mechanisms underlying these changes are clear; the aortic systolic and diastolic pressures, higher than those in the pulmonary artery, result in a flow of blood from the former into the latter in diastole as well as in systole. Accordingly, in an attempt to maintain peripheral flow, an increased systolic aortic pressure must be produced, and since the diastolic aortic pressure falls because of the runoff of blood into the ductus, the blood pressure measurements obtained are those of aortic insufficiency; the peripheral vascular changes must also be the same (page 287). In the case of a small ductus the additional increases in aortic pressure and blood flow caused by exercise may be necessary to bring out these signs as well as the diastolic murmur, since at rest the pressure difference between aorta and pulmonary artery is a good deal smaller in diastole than in systole.

It is also clear that the work of the right ventricle remains close to normal, since the shunted blood does not pass through it, that of the left ventricle is greatly increased. Accordingly, left-sided cardiac enlargement and left-axis deviation in the electrocardiogram occur as a rule. The systemic manifestations of the disorder depend

tion of respiratory gases in blood in the lungs and obtained data that indicated a very large flow of blood through the lungs in their patients. Keys (1941) attempted to justify on mathematical grounds the use of the acetylene method for measuring the systemic (nonpulmonary) flow in patients with this disorder; he concluded that the peripheral flow was usually normal and occasionally diminished. The data of Starr and Jonas (1943), obtained by means of the ballistocardiograph, are probably not reliable when the ductus is open. These authors themselves recognize the fact that their method leads to overestimates of cardiac output under these circumstances, and their conclusion that it measures systemic flow alone does not appear to be justified. They found normal values for cardiac output in their patients with the ductus closed; these data are as reliable as any obtained by that method.

In 1941, Eppinger, Burwell and Gross published the results of their studies made by means of the direct Fick method, and more recently, the same clinic has made studies by means of the catheter (Dexter *et al.*, 1946*a*, *b*, 1947). The flow through the lungs is increased, often greatly, and that to the periphery is normal or low. Low peripheral flows occur when a large ductus drains off so much blood as to exceed the ability of the left ventricle to compensate by an increase in its output; from one-third to three-quarters of the output of the left ventricle was found to be shunted back into the lungs. Ligation of the ductus restores the circulation to normal (Eppinger *et al.*, 1941).

Venous pressure. — Eppinger *et al.* (1941) noted no deviation of venous pressure from the normal.

Right heart pressures. — Right auricular, right ventricular and pulmonary arterial pressures are all normal or borderline (Dexter *et al.*, 1946*a*, *b*, 1947).

Arterial pressure and pulse. — Many patients with patent ductus arteriosus show the peripheral signs of aortic insufficiency, including the changes in arterial blood pressure (Eppinger *et al.*, 1941). Megibow and Feitelberg (1948) described a specific pulse pattern in patent ductus arteriosus.

Vital capacity. — In spite of the shunting of large amounts of blood through the lungs, no reduction in vital capacity occurs (Eppinger *et al.*, 1941).

through the lungs also occurs (Dexter *et al.*, 1947). In patients with Fallot's tetralogy, the presence of pulmonic stenosis causes a decrease in flow through the pulmonary artery (Bing *et al.*, 1947*a*; Dexter *et al.*, 1947; Howarth *et al.*, 1947). The systemic flow is, however, usually normal, blood passing from the right ventricle directly to the left ventricle or aorta, some blood enters the lungs from arteries in the chest, running down over the pleura, that is, there is a collateral circulation. In Eisenmenger's complex, where pulmonic stenosis is absent, the pulmonary arterial and capillary flow is also lower than the systemic; an unexplained increase in pulmonary vascular resistance apparently gives rise to this phenomenon Bing *et al.*, 1947*b*, Handelsman *et al.*, 1947) The output of each ventricle in cases of ventricular septal defect or of overriding of the aorta varies with the amount of shunting and, when pulmonary stenosis is present, with its degree. The blood flow through the lungs, that is, the output of the right ventricle plus blood flowing through collaterals, may be greater than, equal to, or less than the flow to the periphery, that is, the output of the left ventricle. Unless the flow through the lungs is less than the systemic flow, Blalock's (1945, 1946) operation should not be done (Dexter *et al.*, 1946*a*, *b*) Pulmonary flow increases during exertion in patients with isolated septal defects but not with tetralogy of Fallot (Handelsman *et al.*, 1947).

Circulation time. — The arm-to-tongue time may be greatly diminished, since some of the blood returning from the arm does not pass through the lungs when the shunt is from right to left (Bain, 1934; Benenson and Hitzig, 1938, McGuire and Goldman, 1937, Prinzmetal, 1941). In such instances, the end point following the injection of ether into an antecubital vein may be tingling of the face rather than ether on the breath However, the circulation time need not be reduced in all cases (Bain, 1934; McGuire and Goldman, 1937; Myer, 1932; Prinzmetal, 1941). Prinzmetal (1941) has used measurements of the circulation time to calculate the approximate size of the shunt.

Right heart and pulmonary arterial pressures. — In the case of auricular septal defects the right auricular pressure is normal and the right ventricular normal or questionably increased (Brannon *et al*, 1945). The left auricular pressure is slightly above that of the right auricle (Cournand *et al.*, 1947). The right ventricular and pulmon-

on how much of the blood is shunted off into useless circulation through the lungs, with the resultant deprivation to the peripheral tissues. The patients may exhibit retarded growth and development and may complain of variable amounts of exertional weakness and dyspnea. The dynamic changes of the disorder and their physical consequences are reversed by ligation of the patent ductus.

2. *Septal Defects. Morbus Caeruleus*

Congenital septal defects vary greatly in size and location, and may occur alone or in association with other congenital cardiovascular malformations of various degrees of complexity and severity. Often the precise or complete anatomical diagnosis is not made during life, so that the fairly large number of studies made in patients of this type do not yield a homogeneous body of data. In addition, some of the patients studied had congestive failure, while others did not. Another fact to be borne in mind is that many of the patients studied are in the younger age groups, for which normal standards for circulatory and respiratory function are not established.

Cardiac output. — The presence of a septal defect causes in some cases an almost immediate recirculation through the lungs of some blood that has once gone through them, while in most instances where cyanosis is present, some blood returning to the right auricle is not passed through the lungs at that time. Accordingly, the methods for measuring cardiac output that measure the flow through the lungs cannot be expected to give intelligible results. Moreover, where the shunt is from left to right, the flow through the lungs may be much greater than that to the periphery. Studies bearing on cardiac output, made by older methods, have been reported by a number of authors (1). More recent studies by means of the catheter have, for the first time, afforded precise data of this type. Thus, in the case of auricular septal defect, there is a normal peripheral flow, but an increase in flow through the lungs of approximately 100 per cent (Brannon *et al.*, 1945; Dexter *et al.*, 1947; Howarth *et al.*, 1947; Handelsman *et al.*, 1947). In the case of uncomplicated ventricular septal defects a large flow of blood through the shunt and then

roughly with the degree of hyperventilation (Blalock and Taussig, 1945; Dautrebande *et al.*, 1929; Hitzenberger and Tuchfeld, 1931; Richards, 1931). The venous blood carbon dioxide content is normal (Pearce, 1921); however, if hyperventilation is severe, it may be lowered (Hitzenberger and Tuchfeld, 1931). The blood pH may be slightly increased (Dautrebande *et al.*, 1929) under the latter conditions.

Deviations from the normal blood gas concentrations are largely reversed by Blalock's (1945, 1946) operation; this finding demonstrates the primary role of decreased pulmonary blood flow in the above-discussed phenomena.

Blood volume; erythrocyte fragility.—The occurrence of polycythemia, as manifested by high erythrocyte counts and hematocrit values, is well known to occur in congenital heart disease characterized by persistent cyanosis. However, these conditions give no true indication of changes in the blood volume, since the plasma volume is said to be low (Blumenfeldt and Wollheim, 1927; Hallock, 1940; Myer, 1932). The red cell volume is nevertheless elevated (Blumenfeldt and Wollheim, 1927; Hallock, 1940; Weber and Dorner, 1911); the same is true of the total blood volume (Hallock, 1940; Hitzenberger and Tuchfeld, 1929; Weber and Dorner, 1911; Nelson *et al*, 1947) Taussig and Blalock (1947) have correlated the occurrence of polycythemia with arterial blood oxygen saturation; when the latter falls below seventy per cent, the erythrocyte count increases. Increased fragility of erythrocytes has been reported by Greenthal and O'Donnell (1921) in two patients with cyanosis due to congenital heart disease The increases in blood red cell count, hematocrit and oxygen capacity resemble those seen at high altitudes (page 109), suggesting a similar mechanism However, the plasma volume is not appreciably different from normal at high altitudes and the fragility of the red cells is decreased, both of which changes are different from those seen in patients with morbus caeruleus.

Blood carbonic anhydrase.—A normal level of blood carbonic anhydrase activity has been reported in an infant with congenital heart disease and cyanosis (Stevenson, 1943). Clearly much additional information is necessary.

Peripheral vascular system.—One report (Rominger, 1920) re-

ary artery pressures are also normal in instances of ventricular septal defect (Dexter *et al.*, 1947); however, a large defect in the ventricular wall results in elevation of the pulmonary arterial pressure (Blalock, 1946) and in the right ventricular pressure (Dexter *et al*, 1946*a*, *b*). In the case of Fallot's tetralogy, the presence of pulmonic stenosis raises the right ventricular pressure (Bing *et al.*, 1947*a*; Dexter *et al.*, 1947) but the pulmonary arterial pressure remains normal or may fall. In Eisenmenger's complex the right ventricular and pulmonary arterial pressures are very greatly increased, for reasons not clear at present (Bing *et al.*, 1947*b*).

Lung volume and its subdivisions. — The residual, reserve and complemental air volumes are normal in uncomplicated cases, as is the vital capacity also (Myer, 1932; Richards, 1931).

Respiratory dynamics. — The respiratory rate (French *et al.*, 1909) and minute volume are increased above normal (Pearce, 1921; Campbell and Poulton, 1927; Blumenfeldt and Wollheim, 1927; Dautrebande *et al.*, 1929; Bing, 1947*a*, *b*); they are not lowered by inhalation of oxygen (Campbell and Poulton, 1927). The alveolar air carbon dioxide is reduced as a consequence of hyperventilation in this disorder (2, Richards, 1931).

Blood gases. — In the case of auricular septal defects significant changes in arterial blood oxygen do not occur (Brannon *et al.*, 1945). However, the right atrial blood is arterialized (Brannon *et al.*, 1945; Geiger *et al.*, 1946; Johnson *et al.*, 1947). This finding is diagnostic of the condition With simple ventricular defects, on the other hand, the right ventricular blood contains more oxygen than that in the auricle (Baldwin *et al*, 1946; Dexter *et al.*, 1947; Johnson *et al.*, 1947) because of the flow of blood from the left to the right ventricle In cases of Fallot's tetralogy or Eisenmenger's complex, lowering of arterial blood oxygen saturation has long been known (3; Taussig and Blalock, 1947), it is not influenced by oxygen therapy. During exercise the arterial blood oxygen saturation falls still lower (Blalock, 1946; Bing *et al*, 1947*a*, *b*, Montgomery *et al.*, 1948; Gullickson *et al*, 1948). The lowered arterial oxygen content is a consequence of admixture in the left ventricle of unoxygenated blood, for pulmonary capillary and venous blood is normal (Dexter *et al.*, 1946*b*, Handelsman *et al.*, 1947).

The arterial blood carbon dioxide content is lowered, varying

degrees of exertional weakness and dyspnea and, if the defect is large, retardation of growth and development. Cardiac decompensation may ultimately develop. The occurrence of cyanosis of the persistent type in this group of patients is the consequence of pulmonary congestion developing during congestive failure. Attacks of cyanosis may, however, occur from the first, when the intrapulmonary pressure is raised by coughing, straining, crying, and so on, thus elevating the pressure in the right auricle and reversing the prevailing flow so that deoxygenated blood enters the left side of the heart directly and is passed to the periphery.

Simple ventricular septal defects cause similar dynamic changes and may give rise to similar manifestations in general. The diagnosis here is established by the finding of normally oxygenated blood in the right auricle and overoxygenated blood in the right ventricle. If the defect is large *the right ventricular pressure may be elevated.*

Pulmonic stenosis of high degree, or overriding of the septum by the aorta, give rise to persistent cyanosis from the start The various congenital cardiac disorders that are associated with persistent cyanosis may be grouped together for purposes of discussion under the names "morbus caeruleus" or "maladie bleue" The occurrence of cyanosis consequent to admixture of venous blood with arterial, and exaggerated by polycythemia, has been discussed by Lundsgaard and Van Slyke (1923). Of even more interest is the fact that patients with morbus caeruleus may have normal lungs (page 276) and yet show exertional dyspnea. The importance of lactic acidosis in the exertional dyspnea of congenital heart disease has been stressed by Hallock (1938, 1939) A parallel to induced anoxia in normal subjects who also show abnormally elevated blood lactate after exercise (page 87) suggests itself. It is not unreasonable to conclude, therefore, that since lactic acidosis consequent to tissue anoxia causes dyspnea in congenital heart disease, it is also a factor favoring dyspnea in chronic congestive heart failure; this conclusion reëmphasizes the chemical factors in the genesis of such dyspnea. However, whereas dyspnea is bettered by inhalation of oxygen in pulmonary (page 314) and cardiac patients (page 191), no such favorable response occurs in morbus caeruleus, since the tissue anoxia here is consequent to mixing of venous and arterial blood Blowing off of carbon dioxide from the alveolar air and arterial blood has been held

cords dilatation of the venous loop and slowed flow in the capillaries of the nail beds in cyanotic congenital cardiacs, while Blumenfeldt and Wollheim (1927) found no such change. It is to be expected that the presence of polycythemia would result in an increase in the number of visible capillaries, widening of their lumina and slowing of flow in them. Additional studies should be made, especially since calculations have been recorded by Bing *et al.* (1947*a*) which suggest the occurrence of changes in peripheral resistance.

Blood lactate; oxygen debt. — Although the resting blood lactate level is usually normal in morbus caeruleus, abnormally large rises occur in exercise, the rise paralleling dyspnea (Hallock, 1938, 1939). Oxygen debt after exercise is large (Petersen *et al.*, 1921).

Symptoms — As has already been noted, the clinical manifestations of septal defects vary with their location, their size, and the presence or absence of associated anomalies of various types. Simple interauricular defects are easiest to understand. Here blood leaving the left auricle passes in part to the left ventricle and in part to the right auricle. That which enters the left ventricle is distributed throughout the body in a normal manner and the peripheral flow is usually normal. The blood that enters the right auricle from the left, apparently because of a small difference in pressure, goes to the right ventricle, through the lungs and back to the left auricle. The blood passing through these three chambers is joined by that returning from the periphery and the flow through this short circuit is increased to a variable degree; it may be twice normal. Accordingly, dilatation of these three chambers and hypertrophy of the right ventricle may be marked; the pulmonary artery is dilated. Enlargement of the heart to the right, and right-axis deviation in the electrocardiogram are the rule. Dilatation of the auricles may be enormous and lead to confusing roentgenograms. A high incidence of partial heart block and auricular fibrillation occurs, in contradistinction to other types of congenital heart disease, where arrhythmias are uncommon; the mechanisms underlying these arrhythmias are probably similar to those that occur in mitral stenosis (page 285).

The diagnosis is established by the finding of blood abnormally well oxygenated in the right auricle, thus demonstrating admixture of the blood from the left auricle. The systemic effects of auricular septal defect consist, like those of patent ductus arteriosus, in varying

they are associated with a high basal metabolic rate, so that the arterio-venous oxygen difference remains normal. Stewart *et al.* (1938, 1941) reported a slight decrease in cardiac output in one patient.

Circulation time. — The arm-to-tongue time is within the normal range usually (Blumgart *et al*, 1931; Stewart *et al*, 1938, 1941, 1944); the arm-to-leg time tends to be prolonged (Blumgart *et al.*, 1931; Stewart and Bailey, 1941). The latter finding appears to be the consequence of the long, winding path which blood from the heart must traverse to reach the foot.

Venous pressure. — The venous pressure is normal in the absence of congestive failure (Stewart *et al.*, 1944).

Peripheral blood flow. — The peripheral blood flow as a whole is, like the cardiac output, normal or somewhat increased (Stewart *et al*, 1944). The flows through the arm (Lewis, 1933, Pickering, 1935; Printzmetal and Wilson, 1936) and leg (Lewis, 1933), measured plethysmographically, are normal, as are the arteriovenous oxygen differences in the arm and leg (Blumgart *et al.*, 1931). Bing *et al.* (1948) found arm blood flow much increased and leg blood flow somewhat lowered. Accordingly, it must be concluded that although blood going to the legs takes a long route, the volume of blood flowing through the lower extremities is normal, at least at rest That it may be inadequate during exertion is suggested by the fact that intermittent claudication of the leg muscles may occur; measurements made during or shortly after walking are, however, not available.

Tissue gas tensions. — Fragmentary studies in one patient record low oxygen and high carbon dioxide tensions in the tissues (Seevers *et al*, 1936).

Femoral arterial pulse. — The pulse over the femoral artery is, as expected, retarded (Lewis, 1933; Railsbach and Dock, 1929; Woodbury *et al.*, 1940; Galdston and Steele, 1948), and the pulse wave is flat and smooth (Woodbury *et al.*, 1940; Megibow and Feitelberg, 1948). The pulse may feel weak or be impalpable.

Renal vascular dynamics. — The renal blood flow, as measured by the inulin clearance, is low, but glomerular filtration is normal, so that the efferent arterioles probably are constricted (Friedman *et al*, 1941). The decreased blood flow in the kidneys and low pulse pressure that must exist in the renal arteries might result in a situation analogous to that studied extensively by Goldblatt.

by some to be a consequence of reflexes from congested lungs, but morbus caeruleus offers an example of a similar hyperventilation in cardiac disease with no congestion of the lungs; indeed, circulation through the lungs may be diminished. Tissue anoxia, consequent to low arterial oxygen saturation, appears to be the mechanism for hyperventilation in patients with congenital heart disease without cardiac decompensation. The manifestations of morbus caeruleus are the local signs of a cardiac shunt combined with generalized manifestations of chronic anoxia. Retarded growth and development and a poor nutritional state are commonly found in cyanotic patients with congenital heart disease Although inadequate oxygenation of tissues is usually considered the mechanism responsible for these manifestations, it is not unlikely that impaired gastro-intestinal function, as discussed elsewhere (page 136), is also important.

Marked pulmonic stenosis may so impede flow to the lungs as to enhance the symptomatology. Under these circumstances, it is possible to secure some degree of improvement by anastomosing a major branch of the aorta to a pulmonary artery (Blalock, 1945, 1946), causing more blood to enter the lungs and thereby increasing the arterial blood oxygen content. This operation should not be done when the pulmonary flow is as large as, or larger than, the peripheral; studies with the catheter should precede the operation.

3. *Coarctation of the Aorta of the Adult Type*

Coarctation (stenosis of the isthmus) of the aorta of the adult type, formerly considered a rare anomaly, is now being recognized with increasing frequency. It is often associated with other congenital cardiovascular malformations but is compatible with a long and active life. The condition is of interest not only because of the extensive and complicated collateral circulation which develops, but also because of the changes in cardiovascular dynamics it causes. Relief by operation has been described (Crafoord and Nylin, 1945).

Cardiac output. — The output of the heart at rest is normal or somewhat increased (Lequime, 1940; Grollman and Ferrigan, 1934; Stewart and Bailey, 1941; Bing *et al.*, 1948); when increases occur

which is consistent with the view expressed by Rytand (1938). This mechanism could account for the brachial systolic hypertension, the low systolic pressure found in the legs, however, must be due to the stenosis in the aorta. On the other hand Bing *et al.* (1948), who found no elevation of femoral diastolic pressure in their patients, concluded that the hemodynamic changes found in the legs were entirely due to the effects on blood flow of the obstruction itself. Whatever its mechanism, the hypertension must be regarded as the cause of the arteriosclerosis and congestive failure that may develop in patients with coarctation of the aorta.

Basal metabolic rate.—The basal metabolic rate is commonly found to be elevated (Blackford, 1928, Grollman and Ferrigan, 1934; Stewart and Bailey, 1941; Ulrich, 1932), although the mechanism responsible for this finding is unknown, it may be similar to that which often causes elevation of metabolic rate in patients with essential hypertension.

Symptoms.—Aside from clinical manifestations of associated congenital anomalies, the complaints and physical signs of coarctation of the aorta fall into two main groups. (i) those of hypertension, including headache, palpitation, cardiac enlargement, generalized arteriosclerosis and congestive failure and (ii) those of mild or moderate peripheral vascular insufficiency, including cold feet, intermittent claudication and decreased or absent pulsations in the arteries of the legs; gangrene does not develop Although many patients with this disorder live long normal lives, many others die, principally of congestive failure and cerebral hemorrhage. The condition can successfully be relieved by operation (Crafoord and Nylin, 1945).

4. *Acquired Valvular Disease*

Precise characterization in *quantitative* terms of the dynamic effects of acquired, or any other, valvular lesions in man is beset with difficulty. Accuracy of diagnosis of the presence of such lesions is not possible. Estimation of the severity of a lesion from physical signs is often grossly inaccurate. The common association with valvular lesions of myocardial damage or insufficiency confuses the

Arterial blood pressure.—A diagnostic finding in patients with coarctation of the aorta is systolic hypertension in the arms and normal systolic pressure or systolic hypotension in the legs; in rare instances the various arterial pressures may all be normal (King, 1937). The brachial systolic pressure is usually between 140 and 170 mm-of-mercury. The diastolic blood pressure, on the other hand, is the same, or not markedly different, in the arms and legs (4; Woodbury *et al.*, 1940; Galdston and Steele, 1948); it usually ranges between 85 and 100 mm-of-mercury. On the other hand Crafoord and Nylin (1945) and Bing *et al.* (1948) found no elevation of diastolic pressure in the leg. Steele (1939) showed in animals that a clamp on the aorta above the renal veins resulted in an elevation of the diastolic pressure in the legs as well as in the upper parts.

In patients with coarctation of the aorta, the brachial arterial pressure is elevated after work, but that in the legs is unchanged (Crafoord and Nylin, 1945); after relief of the condition by operation, the pressure in the legs also rises during exertion. Lewis (1933) felt that the hypertension in the arteries above the stenosis developed in order to maintain an adequate flow of blood distal to the constriction, but against this concept is the fact that hypertension does not develop in patients with circulatory insufficiency in the legs consequent to arterial disease.

A considerable body of work done on animals shows that when the arch of the aorta is clamped, an immediate rise in brachial blood pressure occurs (Barcroft, 1931*a*, *b*, 1933; Barcroft and Formijne, 1934; Brotchner, 1939); however, Page (1940) showed this rise to be temporary. Recently, Rytand (1938) concluded, on the basis of the results of experiments in animals, that the persistent generalized diastolic hypertension of coarctation of the aorta was a Goldbatt phenomenon, that is, a humoral phenomenon, which occurred as a consequence of renal ischemia. This concept is supported by the finding of similarly elevated diastolic blood pressure levels in the brachial and femoral arteries of patients with coarctation of the aorta and also by the fact that after operation approximately a month must elapse before the hypertension disappears (Crafoord and Nylin, 1945). Although a neurogenic mechanism for the hypertension of the coarctation was suggested by Prinzmetal and Wilson (1936), Pickering (1935) concluded that a humoral mechanism was responsible,

Mitral stenosis. — A number of authors have studied the circulatory dynamics in patients with mitral stenosis (5; Cossio and Berconsky, 1939; Stewart *et al.*, 1938); some have stated that the cardiac output is often low. It is difficult, however, to evaluate these data, since the dynamic effects of the valve lesion are identical with some of those that occur as a consequence of myocardial insufficiency, and the latter may have been present in some of the patients studied. Bloomfield *et al.* (1946), in a study made by means of the catheter, found the systolic right ventricular pressure elevated; the diastolic was normal. The right auricular pressure was also normal The very high venous pressures found by Cossio and Berconsky (1939) and explained as a consequence of obstruction of the superior vena cava have not been found by other workers

The symptoms of mitral stenosis are, as expected, dyspnea on exertion even before myocardial insufficiency develops Such exertional dyspnea may be present for years, or even decades, before frank failure makes itself manifest, in some instances, the circulation time through the lungs may be prolonged because of pulmonary stasis, even in the absence of myocardial weakness. This dyspnea due to mechanical factors need not have the same unfavorable significance as dyspnea consequent to myocardial insufficiency. It is worthy of note that even though pulmonary engorgement and increased pulmonary vascular pressure may be present to a marked degree, severe enough to cause recurrent hemoptyses, attacks of acute pulmonary edema are relatively uncommon. The prolonged pulmonary congestion of mitral stenosis may ultimately result in lesions in the pulmonary vascular tree (Parker and Weiss, 1936) or in fibrotic perivascular lesions (Moschcowitz, 1930; Parker and Weiss, 1936) known to pathologists as "brown induration of the lungs." The brown coloration is probably due to the presence of pigment either free or in phagocytes, that is, the "heart failure cells." When fibrosis of the lungs develops in significant degree, clubbing of the fingers, polycythemia and the manifestations of pulmonary fibrosis in general (page 302) may appear

Auricular fibrillation is recognized as common in mitral stenosis. The origin of this arrhythmia in general is not clearly understood by many clinicians. Auricular fibrillation develops when auricular conduction is slowed and the refractory period of the auricular myocar-

picture, as do the facts that in a majority of instances more than one valve is involved and more than one type of damage to each valve exists. Accordingly, the interpretation of many of the published data is most insecure.

On the other hand, it is possible to formulate certain conclusions as to the effects of valvular lesions in general. For instance, it is apparent that stenotic lesions place a variable amount of strain on the ventricle which is situated in a retrograde position; it has actually been shown (page 276) that the right ventricular pressure is elevated in patients with pulmonic stenosis and also in those with mitral stenosis (Bloomfield *et al.*, 1946). Therefore, according to the formula of Evans and Matsuoka (1915), $W = OP + \frac{1}{2}\ (w/g)V^2$, the work W of the ventricle is increased because the pressure P is greater. In this equation, O is the output of the heart, so that the term OP represents the output and pressure factors in blood flow and the term $\frac{1}{2}\ (w/g)V^2$ represents the velocity factor. Ordinarily, the latter is equal to only approximately 2 per cent of the total cardiac work, but, in the presence of stenotic lesions, interference with the ability of the ventricle to impart velocity to the blood results in an increase in the velocity factor, so that it may rise to 20 per cent of the work of the heart (Evans and Matsuoka, 1915). These factors become exaggerated during exertion, so that during work the cost to the heart of maintaining the necessary increases in blood flow and blood pressure may be so much greater than normal as to render its attainment impossible In addition, the fact that the cardiac work is increased at rest reduces the reserve to be used during exertion.

These theoretical considerations have had ample verification in the demonstration in man that patients with valvular disease often exhibit a subnormal increase in cardiac output during work (page 8) and an increased oxygen debt (page 91) and flow debt after it (page 28). A similar state results in patients with regurgitant lesions, but here the strain on a ventricle is a consequence of the fact that it must put out more blood and develop a higher pressure than normal in order to maintain a normal flow ahead.

Another fact to be borne in mind is that the organ immediately retrograde to a damaged valve usually shows the greatest and the earliest evidence of damage.

measured with a foreign gas by means of the Fick principle, with the output of the left ventricle, measured by other means, normally the two are equal. Since none of the methods used by these authors yields results of absolute accuracy, their conclusions must be accepted with a good deal of reservation. The amount of regurgitation in aortic insufficiency has been calculated by these authors to range between 15 and 40 per cent of the output of the left ventricle The resulting increase in cardiac work favors the development of failure, although myocardial weakness due to damage to the heart muscle itself is more important in many instances The inefficiency of the heart in aortic insufficiency probably limits the increase in cardiac output that occurs in exercise, for Abramson *et al* (1942) found that work led to a more persistent increase in peripheral flow than normal, as if a debt had to be discharged.

The peripheral vascular phenomena of aortic insufficiency have interested clinicians for many decades. The low diastolic pressure is a direct consequence of regurgitation The collapsing pulse has been studied extensively and, contrary to the opinion held by most clinicians, it is not the direct result of regurgitation of blood from the aorta and main arteries. Stewart (1908) showed that most of the sharp fall in blood pressure in aortic insufficiency occurs during systole, and this has recently been corroborated by studies made in man by means of arterial puncture (Kotte *et al*, 1944). This finding led Hewlett and Van Zwaluwenburg (1913), and many others since, to conclude that peripheral vasodilatation is present in aortic insufficiency, so that blood quickly runs off into the periphery. This conclusion is reasonable, for in effect the left ventricle and the peripheral circulation are in competition for the blood in the aorta in patients with aortic insufficiency; peripheral vasodilatation would favor the flow of blood to the periphery However, Hewlett and Van Zwaluwenburg (1913) found a regurgitant rather than a forward flow in the arteries The fact that Abramson *et al* (1942) observed no constant deviation from the normal value for *total* flow through the arm or leg in aortic insufficiency is not helpful in this regard. Wiggers (1931) reviewed the experimental data available and concluded that peripheral vasodilatation does not occur in this disease, he felt that aortic regurgitation results in a change in ventricular dynamics so that the curve of intraventricular pressure rises more steeply and to a higher

dium is shortened. How the first of these is brought about is not known, but it is established that vagal action accomplishes the second. Evidence for the role of vagal hyperactivity in inducing auricular fibrillation in general and in mitral stenosis in particular is presented in detail elsewhere (Altschule, 1939, 1945). It has been pointed out that a majority of patients have other evidences of vagal hyperactivity before the onset of auricular fibrillation. The origin of these vagal impulses is obscure, but it is possible that they are reflex and arise from overdistention of the great veins, active rheumatic lesions in the great veins or aorta, congestion of the lungs, or other sources of vagal reflexes.

Aortic stenosis. — In addition to the typical murmur, which requires no discussion, there are striking peripheral signs in patients with marked aortic stenosis, namely, bradycardia, small pulse pressure, systolic hypotension, diastolic hypertension, small pulse and a flat pulse wave. The bradycardia cannot be explained, although prolongation of the period of ventricular ejection may be important in that it would necessarily tend to decrease the number of systoles possible per minute, if diastole remained unchanged. The other signs are so strikingly like those that obtain below the constriction in coarctation of the aorta as to suggest a similar mechanism (page 281). The low systolic pressure is due to the presence of the stricture itself, but the elevated diastolic pressure may be the consequence of a Goldblatt phenomenon, much like the one that Rytand (1938) discussed in relation to coarctation. The result is a decreased pulse pressure and a small pulse. Attacks of syncope, not infrequently in relation to exertion, may occur. During exertion the muscles drain off an increased portion of the circulation and, since increases in cardiac output are limited, other parts of the body, including the brain, suffer. Other mechanisms, as yet not understood, may also play a part. Angina pectoris is also common; this is probably related to narrowing of the coronary ostia by scar tissue.

Aortic insufficiency. — Although patients with compensated aortic insufficiency show a normal cardiac output at rest, the output of the left ventricle is actually increased in order to compensate for regurgitation of blood past the damaged valves Bazett *et al.* (1941) and Keys and Freidell (1939*a*, *b*) have attempted to estimate the amount of regurgitation by comparing the output of the right ventricle, as

diastolic aortic pressure. The occurrence of attacks of pulmonary edema and, in many instances, the rapid progression of congestive failure when it occurs are both not well understood. Paroxysmal attacks of sinus tachycardia together with hypertension may be very distressing (Lewis, 1931); their mechanism is obscure but may be related to the apparent loss of depressor reflex mechanisms found in patients (Hamilton *et al.*, 1944) and also in experimental animals (Brewer *et al.*, 1934) with aortic insufficiency.

Rheumatic tricuspid disease. — Organic disease of the tricuspid valve is of interest to clinicians because of the striking clinical manifestations, including marked venous pulsations, early development of cirrhosis and the unusual coloration of the skin consequent to the simultaneous occurrence of icterus and cyanosis In addition, this valve lesion is of considerable theoretical importance since it causes very high venous pressure which may persist for years without giving rise to edema, and it may be associated with some degree of orthopnea, even in the absence of myocardial insufficiency The condition is relatively uncommon; hence, data bearing on cardiorespiratory function are scanty.

(1) *Cardiac output* Normal values of cardiac output obtain when the heart is compensated (Altschule *et al*, 1937, 1940); when congestive failure develops the usual fall in cardiac minute volume output occurs.

(2) *Circulation time* The arm-to-tongue time is long in the absence of congestive failure and becomes longer when failure supervenes (Altschule *et al.*, 1937, 1940). The increase that occurs before the onset of failure is probably entirely in the venous segment, there are, however, no data bearing on this point.

(3) *Right heart pressures.* The systolic right ventricular pressure is elevated but the diastolic is normal (Bloomfield *et al*, 1947), findings which are difficult to interpret since they may be due to mitral stenosis; organic rheumatic tricuspid disease without mitral disease is rare (Altschule and Budnitz, 1940). The right auricular pressure is also elevated (Bloomfield *et al.*, 1946); the gradient between auricular and ventricular pressure may be reversed during part of the cardiac cycle. The right auricular pressure rises in inspiration for reasons not known (Lauson *et al.*, 1946).

(4) *Venous pressure.* High venous pressures are found in all pa-

level than normal, with an almost equally steep fall so that the pressure is well on its way back to the base line *before the end of systole.*

The concept that peripheral vasodilatation occurs in aortic insufficiency outwardly receives support from the common finding of capillary pulsation in this disease. Lewis (1924) and Heimberger (1925) showed that vasodilatation caused the appearance of this phenomenon. Wiggers (1931), on the other hand, demonstrated by means of artificial model circulatory systems that aortic insufficiency can cause capillary and even venous pulsation in spite of the absence of any change in peripheral resistance. There has been some controversy as to which vessels give rise to the phenomenon of capillary pulsation; Boas (1922), Fischl (1923) and Hisinger-Jägerskiöld (1924) found no abnormal pulsations in the capillaries on direct microscopic examination in patients with aortic insufficiency. Secher (1922) and a later report by Boas (1924) describe such pulsations as inconstant. However, the observation of pulsation, pulsatile flow and even regurgitation in the capillaries, made by means of direct miscroscopy by Jürgensen (1920), Freedlander and Lenhart (1922), Sumball (1923), Weiss and Dieter (1920), and Lewis (1924), are convincing. *Accordingly, it must be concluded that the rhythmic flushing of* aortic insufficiency is consequent largely to changes in capillary circulation; the abnormal pulsations seen in venules must also play an important role.

The concept of "free aortic regurgitation," based on the finding by auscultation of a diastolic blood pressure at or near zero, is probably erroneous, for direct arterial puncture has shown that values obtained by the auscultatory method are much too low in many or most patients with aortic valvular insufficiency (Kotte *et al.*, 1944; Ragan and Bordley, 1941). Another clinically accepted concept, namely, that a femoral arterial pressure higher than the brachial is diagnostic *of aortic insufficiency, has been negated by the work of* Kotte, Iglauer and McGuire (1944), who showed that this difference also exists in a majority of normal individuals.

Symptoms in patients with aortic insufficiency include severe discomfort due to palpitation, probably consequent to widened *pulse* pressure. Angina pectoris is also common and is probably related to myocardial ischemia secondary to low diastolic arterial pressures; filling of the coronary vessels is considered to be governed largely by

during exertion. In spite of the marked elevation of venous pressures persisting for years, visible edema may be minimal or even absent in some patients (Friedlander and Kerr, 1936; Altschule and Budnitz, 1940); this finding negates the concept that cardiac edema is due solely to failure of the right ventricle with consequent rise in venous pressure. Reasons for the failure of edema to occur in patients with tricuspid disease include normal cardiac output and renal blood flow, absence of tissue anoxia, and maintenance of normal plasma protein levels. When congestive failure develops, not only does peripheral edema appear, but a large amount of fluid — over a liter — may accumulate in the pericardial space (Altschule and Budnitz, 1940) This accumulation of fluid may be consequent in part to the very high venous pressures in the coronary sinus, which drains into the right auricle; the coronary sinus may be found greatly dilated at autopsy. The accumulation of these large volumes of fluid in the pericardium may give rise to signs of pericardial tamponade, with falling arterial blood pressure and pulse pressure, increasing venous pressures and diminution of the force of venous pulsations. An interesting observation on the orthopnea that may occur in triscupid disease in the absence of myocardial insufficiency has been reported (Altschule and Blumgart, 1937); in a patient studied, lowering the head of the bed caused a smothering sensation when the visible venous engorgement rose to a level corresponding approximately to that of the respiratory centers in the brain.

The cyanosis of tricuspid disease is not due to abnormal deoxygenation of capillary blood, but rather to increased prominence of cutaneous veins and venules (Altschule and Blumgart, 1937) It has been stated that the presence of the tricuspid lesion protects the patient from the consequences of the commonly associated mitral stenosis, as evidenced by the long life with relative comfort that patients with a combination of the two lesions may enjoy when apparently in congestive failure This view, however, neglects the fact that venous engorgement, exertional dyspnea and even edema and orthopnea are the consequences not of myocardial insufficiency but rather of a nonprogressive or very slowly progressive physical impediment to the entry of blood into the right ventricle, so that it is erroneous to diagnose myocardial insufficiency in such instances. When the latter finally occurs, dyspnea, orthopnea and edema are extreme, treatment

tients with well-marked stenosis or insufficiency (Robb and Weiss, 1934; Friedlander and Kerr, 1936; Altschule *et al.*, 1937, 1940; Bloomfield *et al.*, 1946), rising higher with congestive failure. The veins pulsate with each beat of the heart, the degree of pulsation varying roughly with the amount of valvular insufficiency; pulsations may cause a rise in pressure of 2 cm-of-water or more. The pulsations may be damped by the occurrence of myocardial insufficiency, with consequent overfilling of the veins even in diastole, and also by the development of pericardial tamponade (Altschule and Budnitz, 1940). The pulsations usually manifest two phases, presystolic and systolic; since the former are due to auricular contraction, they may disappear in the presence of such arrhythmias as auricular fibrillation or standstill, and nodal rhythm or tachycardia (Friedlander and Kerr, 1936).

(5) *Arterial blood pressure* Tricuspid disease in itself does not influence the arterial blood pressure. Such changes as occur in patients with this disease are consequent to the commonly associated aortic valvular disease, or the pericardial tamponade that may also occur.

(6) *Vital capacity; respiratory dynamics.* The vital capacity may be low in patients with tricuspid disease (Altschule *et al.*, 1937, 1940); interpretation of this finding, however, is difficult, since it may be consequent to weakness, to the reduction of pulmonary expansibility by the presence of an enormously dilated heart, or to pulmonary stasis due to the mitral stenosis that occurs in almost all instances of rheumatic tricuspid disease The respiratory dynamics in the absence of myocardial insufficiency are normal at rest (Altschule and Budnitz, 1940).

(7) *Hepatic function.* Visible icterus as well as elevation of the serum bilirubin are of common occurrence in patients with organic tricuspid disease, the galactose tolerance test is normal (Altschule and Budnitz, 1940).

(8) *Symptoms.* The persistently high venous pressures and the occurrence of marked venous pulsations in tricuspid disease are readily understandable. The cardiac output at rest may, nevertheless, remain normal, enough pressure being built up in the veins to overcome the obstruction to the inflow of blood into the right ventricle. It is doubtful, however, that normal increases in cardiac output occur

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is commonly ineffectual and the course is short. Tricuspid disease is another example of the utility of differentiating between valvular incompetence or some other physical impediment to flow, which is very slowly progressive, and myocardial insufficiency, which in most instances is very disabling and is more rapidly progressive; it is to be understood, of course, that the first may give rise to the second with little or no change in the character but only in the severity of the manifestations.

In the early stages of the syndrome the enlarged liver pulsates synchronously with the neck veins; later, as fibrosis progresses, the liver becomes firmer and smaller and pulsations diminish. In some instances, the clinical manifestations of cirrhosis may dominate the picture, or at least precede those of congestive failure. The occurrence of purpura in a significant proportion of patients with tricuspid disease may be consequent to prothrombin deficiency; no studies bearing on this factor are available.

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Chapter VI

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tent at rest is elevated and the oxygen content is low (Houssay and Berconsky, 1932). Mixing in the lungs is retarded (Roelsen and Bay, 1940). During exercise patients with pulmonary fibrosis are unable to increase the tidal air volume normally (Kaltreider and McCann, 1937); however, the respiratory rate rises markedly, so that the respiratory minute volume is increased to a considerable degree above normal (Bohme, 1939; Kaltreider and McCann, 1937). The latter returns to its resting level slowly after the cessation of exercise. The maximal possible ventilation per minute is reduced (Kaltreider and McCann, 1937). While in normal subjects the response to exercise is a considerable lowering of the ventilation equivalent, that is, the volume of air breathed per hundred cubic centimeters of oxygen consumed, patients with pulmonary fibrosis show only a slight decrease in this respect. The oxygen debt after exercise is large and prolonged (Nylin, 1937, 1938); the variable findings in this respect reported by Schlomovitz *et al.* (1938) reflect the fact that the period of study used by these authors was too short

Blood gases. — The arterial blood oxygen saturation is often low (2; Hurtado *et al.*, 1935*b*), when low it may be restored to or toward normal by the inhalation of oxygen (Richards and Barach, 1934). Exercise results in variable changes in arterial blood oxygen saturation, which may fall markedly at times (Kaltreider and McCann, 1937). The arterial blood carbon dioxide content is normal or high at rest (Houssay and Berconsky, 1932, Hurtado *et al.*, 1935*b*), it may fall somewhat during exercise (Kaltreider and McCann, 1937).

Cardiac output — Data on the output of the heart are scanty; normal values were reported in uncomplicated pulmonary fibrosis by Brooks (1936) and by Ringer and Altschule (1930).

Circulation time. — Normal values for arm-to-tongue and arm-to-lung time have been recorded (Miller, 1936; Piccione and Boyd, 1941). The prolongation of arm-to-tongue time described by Charr and Riddle (1937) is probably an artefact, since they considered the normal time to be 10 to 12 seconds, instead of the range of 12 to 18 or 20 seconds accepted by most authors. The report by Charr and Savacool (1938) of very long ether times in their patients is difficult to accept in the light of other data Possibly their patients were suffering from the complicating factors of cor pulmonale or marked polycythemia.

VII

PULMONARY FIBROSIS

Fibrotic pulmonary changes, severe enough in themselves to give rise to symptoms, may occur in the various types of pneumoconiosis and in extensive unresolved pneumonia, fibroid phthisis, bronchiectasis, healed war-gas poisoning and, in relatively rare cases, in patients with advanced mitral stenosis or scleroderma The altered physiologic findings in such patients are related to the density and extent of the fibrotic process rather than to the etiologic factors involved. The cardiorespiratory dynamics may be modified, however, by the presence of fever associated with an infectious process or by myocardial insufficiency occurring late in the disease.

Subdivisions of the lung volume.—The subdivisions of the lung volume have been studied by many authors (1; Hurtado *et al*, 1935*a*) The functional residual air is normal, while the residual air is normal or somewhat increased. The reserve (supplemental) air is diminished somewhat, indicating loss of elasticity of the lungs. The considerable decrease in complemental air demonstrates impaired expansibility The vital capacity is, of course, greatly diminished and the total capacity is also low.

Respiratory dynamics.—The tidal air is often diminished (Altschule *et al.*, 1941; Houssay and Berconsky, 1932). However, the respiratory minute volume at rest is normal or somewhat increased (Altschule *et al*, 1941; Böhme, 1939; Houssay and Berconsky, 1932; Kaltreider and McCann, 1937); its value is maintained by an elevated rate (Altschule *et al.*, 1941; Houssay and Berconsky, 1932; Kaltreider and McCann, 1937). Inhalation of oxygen lowers the respiratory minute volume in pulmonary fibrosis (Richards and Barach, 1934). The alveolar air carbon dioxide con-

in dead space, so that all of the decrease in the former occurs in that portion used for respiratory exchange.

All factors that lower tidal air volume while leaving unchanged the functional residual air volume, that is, the air left in the lungs after normal respiration, upset the ratio between the two and impair mixing with and diffusion from the latter. The air remaining in the lungs after each breath consequently may contain abnormally high concentrations of carbon dioxide and low concentrations of oxygen. The abnormally large respiratory minute volumes that occur in exercise, and often even at rest, represent in part an attempt to restore these gas tensions to normal; this increased respiratory activity is inefficient as it is effected by an increase in rate, since the tidal air is increased only with difficulty. The increase in rate in itself contributes to dyspnea. Even if compensation at rest is attained it is clear that the amount of increase in respiration that can occur in exercise is limited and accordingly exertional dyspnea occurs. Failure to achieve complete compensation in this manner at rest or during exertion leads to varying degrees of arterial anoxia and carbon dioxide retention, which may also contribute to dyspnea. In addition, it must be borne in mind that fibrous thickening of alveolar walls may impair gaseous diffusion, and that flow of blood through large areas of unaerated, scarred lung may also give rise to anoxia and hypercarbia. The inability to increase tidal air volume normally in exercise leads to a considerable reduction in maximal possible ventilation, so that exercise is particularly likely to cause or increase respiratory decompensation, thereby leading to an increased and prolonged oxygen debt after work.

It is of interest that the application of chest binders in normal individuals may so restrict the tidal air and respiratory minute volumes as to lead to inability to absorb adequate amounts of oxygen in exercise and a consequent increased debt in the recovery period (page 92). The occurrence of this abnormal debt in patients with extensive pulmonary fibrosis probably leads to lactic acidosis, although data bearing on this point are not available. It is important, however, that anoxia even in normal subjects causes abnormally increased respiratory minute volume, oxygen debt and blood lactate (page 87) after exercise. That such lactic acidosis may occur is suggested by the marked hyperventilation and the finding that the arterial blood car-

Venous blood pressure. — Normal values are recorded by most authors (Hurtado *et al.*, 1935*a*; Heise and Steidl, 1938; Charr and Savacool, 1938); however, Charr and Savacool (1938) found some patients with pulmonary fibrosis to have elevated levels.

Right ventricular pressure. — *Judging by the not infrequent occurrence of elevation of right ventricular pressure, that in the pulmonary artery sometimes is elevated, at times even in the absence of the right ventricular dilatation (Cournand et al., 1944; Riley et al., 1948). However, the pressure in the right ventricle is often normal* (Bloomfield *et al.*, 1946). During exercise the pulmonary arterial pressure rises abnormally (Riley *et al.*, 1948).

Arterial pressure. — Arterial pressure is not influenced by the disease.

Blood volume. — Some degree of polycythemia is fairly common in patients with severe pulmonary fibrosis, and the hematocrit and therefore the viscosity may be more or less increased (Brooks, *1936); the plasma volume is normal, however (Brooks, 1936).* Accordingly, the blood volume may be in the normal range or show an increase (Brooks, 1936; Kaltreider *et al.*, 1934). The bone marrow is often anoxic (Berk *et al*, 1948).

Symptoms. — *The normal functional residual air volume* of pulmonary fibrosis shows that there is no lack of space available for respiration in most patients with pulmonary fibrosis. Nevertheless anoxia and hypercarbia occur, they are a consequence of poor mixing in the lungs — the "alveolar hypoventilation" of Houssay and Berconsky (1932) Such poor mixing as occurs in fibrosis is the consequence of a decrease in tidal air volume relative to the normal that may be present at rest, and that becomes manifest or more marked in exercise; marked loss of expansibility consequent to extensive scarring in the lung is largely responsible for this change. A contributory factor is loss of pulmonary elasticity, which may be fairly severe in some instances. Another contributory factor may be dyspnea due to anoxia, which may occasionally make the patient increase his respiratory rate to extreme degrees in an attempt at compensation, with a resultant further decrease in tidal air volume. Normally a quarter or a fifth of the tidal air merely washes out the dead space and does not directly participate in respiration; the diminution in tidal air in fibrosis is not accompanied by a corresponding decrease

Reference has been made elsewhere (page 136) to the fact that anoxia causes pylorospasm, slows gastric emptying, diminishes hunger contractions, depresses gastro-intestinal tone and motility, and may impair absorption. All of the references cited describe studies made in severe anoxia of short duration, mostly in dogs under anesthesia. The validity of the use of these data to explain the anorexia, belching, indigestion, flatulence and constipation that may occur in patients with severe pulmonary fibrosis is not established. Nevertheless, these symptoms may be related to anoxia In addition, it has been shown that inducing in normal subjects elevated blood bicarbonate levels, such as obtain in patients with severe pulmonary disease, gives rise to gastric hyperacidity (Bakaltschuk, 1928, Szilárd, 1930; Browne and Vineberg, 1932); possibly marked carbon dioxide retention caused by severe pulmonary fibrosis may also be an indirect cause of gastric symptoms

Patients with pulmonary fibrosis often appear more plethoric than measurements show them to be It is not unlikely that the excessively high color is a consequence in some instances of carbon dioxide retention, for carbon dioxide is a cutaneous vasodilator.

That patients with severe chronic respiratory insufficiency exhibit a notable tolerance to anoxia and hypercarbia is well known The mechanisms that give rise to this tolerance have not been studied in pulmonary fibrosis, but judging by what occurs in pulmonary emphysema (page 314) the changes that occur include lowering of blood chloride levels and increased blood hemoglobin and carbonic anhydrase concentrations

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Chapter VII

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bon dioxide content in patients with pulmonary fibrosis may fall during exercise, evidences of central respiratory stimulation. This is not conclusive, since severe anoxia and reflexes from the lungs may also result in central respiratory stimulation. However, Crisafulli and Colacresi state (1937), without recording data, that lactate tolerance is impaired in chronic pulmonary disease. If lactic acid does accumulate in the blood in excessive amounts, it must be regarded as one cause of the exertional dyspnea of pulmonary fibrosis.

It must not be concluded that dyspnea is necessarily due only to anoxia and hypercarbia in patients with pulmonary fibrosis. The impaired pulmonary expansibility that results from pulmonary fibrosis in itself favors dyspnea, since it increases the effort required to attain a given tidal air volume. Similarly, the loss of elasticity that may occur may require that expiration become an active process rather than the passive process it is normally.

Pulmonary fibrosis itself may cause no demonstrable change in cardiovascular dynamics; however, pulmonary arterial and right ventricular hypertension may occur. This strain upon the heart may result in cardiac hypertrophy and ultimately in failure. It was formerly believed that pulmonary vascular hypertension in this condition was due to fibrotic perivascular changes which narrowed the vascular bed. More recent evidence (Sharpey-Schafer, 1946; Richards, 1945) shows that the flow through the lungs is normal or increased in patients with cor pulmonale, which suggests that narowing of the bed is not important. Of great interest is the work of Motley *et al.* (1947), which showed that anoxia causes pulmonary vasoconstriction. In passing, it may be noted that this vasoconstriction might, if long continued, give rise to the pulmonary vascular sclerosis seen in pulmonary diseases, much as peripheral arteriolar sclerosis develops in systemic hypertension.

The increased blood flow of anoxia (page 70) may, over a period of years, also constitute a strain Indeed, it may account for the puzzling left ventricular hypertrophy seen not uncommonly in patients with cor pulmonale. When cardiac failure occurs, the clinical picture is modified by the antecedent anoxia, increased blood volume and cyanosis, so that extreme degrees of cyanosis, mental clouding and elevation of venous pressure are found The cardiac output is high relative to the normal, but probably low for the degree of

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1934), since much of the increase in the latter occurs at the expense of the reserve air; the reserve air is low and may fall to zero (2; Christie, 1934). The complemental air is also smaller than normal (3, Hurtado *et al.*, 1934) according to all authors but Siebeck (1910). Accordingly, vital capacity is likewise reduced (4; Christie, 1934); Kountz and Alexander (1929, 1933, 1934) found the vital capacity decreased more in obstructive than in senile emphysema. The total capacity is low or normal, depending upon the relation between increase in residual air and decrease in vital capacity (5; Christie, 1934; Hurtado *et al*, 1933, 1934). All authors agree, however, that the residual and functional residual air volumes are increased, often markedly, relative to the total capacity.

Pulmonary elasticity. — All authors who measured pulmonary elasticity found low values (Christie, 1934, Paine, 1940, von Neergard and Wirz, 1927*a*, *b*), this is to be expected from the marked decrease in reserve air that occurs in pulmonary emphysema.

Intrapleural pressure — The above-mentioned decrease in reserve air should be associated with an increased static intrapleural pressure, and indeed several good studies have demonstrated this increase (6; Christie, 1934), Ameuille's observations (1920) are not in accord with these more thorough studies During respiration the inspiratory intrapleural pressure is more negative and the expiratory more positive than normal (Dean and Visscher, 1941; Paine, 1940).

Mixing in the lungs. — Mixing of gases in the lungs is impaired (7; Cournand *et al.*, 1937, 1941), Darling, Cournand and Richards (1944) demonstrated two different types of mixing defect, one due to a very large residual air volume and another consequent to poor mixing of tidal air associated with decreased pulmonary elasticity. Diffusion across the alveolar walls is normal (Christie, 1934) The alveolar air carbon dioxide content usually is high (Christie, 1934; Cobet, 1924; Dautrebande, 1925; Goggio, 1944; Houssay and Berconsky, 1932); the alveolar oxygen content is often lower than normal (Goggio, 1944; Houssay and Berconsky, 1932).

Respiratory dynamics. — The respiratory minute volume in patients at rest is often increased (8; Kaltreider and McCann, 1937); it may be normal in milder cases (9; Campbell and Poulton, 1926). In exercise it rises abnormally and returns to the resting value slowly (Campbell and Poulton, 1926; Herbst, 1928; Kaltreider and Mc-

VIII

CHRONIC PULMONARY EMPHYSEMA

A large amount of information bearing on respiratory and circulatory functions in chronic pulmonary emphysema has accumulated and, since the findings of almost all authors are in agreement, a satisfactory body of knowledge exists. A few authors have attempted to differentiate between senile and obstructive emphysema, but most have felt that this distinction is not a useful one. In almost all instances the patients with obstructive emphysema who have been studied developed emphysema secondary to asthma; the effects of asthma itself are described in Chapter IX. There is no agreement as to the etiology of senile or nonobstructive emphysema, some authorities believing that changes in the lungs are primary, while others consider that these changes are secondary to a disease of the spine. The former seems the more reasonable, though far from established; it appears that senile emphysema is consequent to loss of elasticity of the lungs with advancing age, much as the vessels lose their elasticity after middle life, the changes in the spine being secondary.

Lung volume and its subdivisions — Although the validity of some of the earlier methods used for measuring residual air has been questioned, there is a remarkable degree of qualitative agreement among various authors as to the findings in patients with pulmonary emphysema. The residual air is greatly increased in volume according to most authors (1, Darling *et al*, 1944); the only discordant findings are those of Bohr (1907) who described it as normal, and of Hurtado *et al.* (1934), who found it normal in senile but not in obstructive emphysema. The functional residual air is also increased, but less so than the residual (Bittorf and Forschbach, 1910; Christie,

expected result in view of the variability of the method. More recently, studies made by cardiac catheterization have shown high values when severe anoxia is present (Richards, 1945; Sharpey-Schafer, 1946) or normal values (Hickam, J. B., and Cargill, 1948) in other instances. The cardiac output increases normally in exercise (Hickam and Cargill, 1948).

Peripheral blood flow. — No systematic studies of peripheral blood flow are available, but a single observation suggests that when anoxia is severe the blood flow in the hands may be diminished; at least it increases when oxygen is breathed, a response that does not occur in noncyanotic individuals (Stewart, 1911).

Circulation time. — Normal or reduced values for arm-to-tongue or -face time are reported by a majority of authors (**10**; Oppenheimer and Hitzig, 1936) in emphysema and also in pulmonary disease in general (**11**; Baer, 1940); the ether time is likewise normal in pulmonary disease (Baer, 1940; Baer *et al*, 1938, 1940), as is the amyl nitrite time also (Gross, 1945) Increased circulation time is recorded by Koch (1922) and also by Kountz *et al.* (1932) in some patients with emphysema, the degree of increase varying with the increase in intrapleural pressure, according to the latter authors

Venous pressure. — The venous pressure is usually within normal limits (**12**, Weiss and Blumgart, 1927), however, it may be elevated in some instances (**13**, Kountz and Alexander, 1934); when elevated, the change is said to be consequent to marked increases in intrapleural pressure. Kountz *et al.* (1929) found it elevated in the obstructive, but not in the senile type. Patients with emphysema may exhibit an abnormal rise in venous pressure after exercise (Schott, 1912).

Right ventricular and pulmonary arterial pressures — The right ventricular pressure may be high at times, although often no deviation from normal occurs (Bloomfield *et al.*, 1946; Cournand, *et al.*, 1944; Battro *et al*, 1949). The pulmonary arterial pressure is often elevated at rest and increases markedly on exertion (Riley *et al.*, 1948; Hickman and Cargill, 1948).

Arterial pressure — The systemic arterial pressure is not influenced by pulmonary emphysema

Blood gases; tissue gas tensions. — The arterial blood oxygen saturation, though often normal, is commonly somewhat low (**14**;

Cann, 1937). The tidal air volume at rest may also at times be normal or occasionally even high (Knipping *et al.*, 1932; Reinhardt, 1912; Staehelin and Schutze, 1912); more often it is found to be somewhat reduced (Campbell and Poulton, 1926; Houssay and Berconsky, 1932; Knipping *et al.*, 1932; Paine, 1940). The respiratory rate is usually somewhat elevated at rest (Staehelin and Schütze, 1912, Kaltreider and McCann, 1937; Houssay and Berconsky, 1932; Campbell and Poulton, 1926; Bittorf and Forschbach, 1910). The increase in tidal air that occurs during exercise is smaller than normal (Campbell and Poulton, 1926; Kaltreider and McCann, 1937); the maximal possible ventilation is accordingly low (Herrmansen, 1938; Jansen, *et al*, 1932, Kaltreider and McCann, 1937; Zaeper and Wolf, 1939). The ventilation equivalent, that is, the volume of air breathed for each hundred cubic centimeters of oxygen absorbed, is often somewhat increased at rest (Herbst, 1928; Knipping *et al.*, 1932); it falls only slightly in exercise (Kaltreider and McCann, 1937) or even rises (Herbst, 1928), whereas in the normal subject it may fall considerably. Exercise is associated with an abnormally small increase in oxygen intake for the work performed, so that the debt after exercise is large and prolonged (Herbst, 1928; Herms and Rüttgers, 1931); the finding of Schlomovitz *et al.* (1938) that the debt is smaller than normal is an error based upon too short a period of study after cessation of exercise. Of great interest is the observation that breathing air enriched with oxygen during exercise increases the intake of oxygen at that time (Herrmansen, 1938; Zaeper and Wolf, 1939); a similar statement was reported for patients with pulmonary disease in general (Marzahn *et al.*, 1936). The total cost of work in oxygen consumption for a given task may be normal or occasionally high (Herms and Rüttgers, 1931); that is, efficiency may be low in some patients.

Cardiac output.—There are few studies on cardiac output and arteriovenous oxygen difference in patients with uncomplicated emphysema; the values obtained by older methods are normal (Dautrebande, 1925; Scott, 1920). The observation that patients with pulmonary disease usually show normal values is based on a study that includes cases of emphysema (Ringer and Altschule, 1930). Starr and Jonas (1943), using the ballistocardiograph, found high, low or normal values for cardiac output in pulmonary disease, not an un-

blood volume have been described in pulmonary emphysema (Hitzenberger and Tuchfeld, 1929; Rowntree and Brown, 1929; Lerman, 1929; Kaltreider *et al*, 1934); the total blood volume is more likely to be increased than the plasma volume. The hematocrit is found to be elevated much less often in emphysema than in pulmonary fibrosis; some of the increase may be consequent to increased cell size (Price-Jones, 1921; Kaltreider *et al*, 1934). When the hematocrit is elevated, an associated increase in oxygen capacity is of course found.

Symptoms. — Clinicians, wont to diagnose the presence and severity of pulmonary emphysema by the shape of the thorax, are often surprised by the lack of correlation between the occurrence of dyspnea and the development of a barrel chest This fact suggests that the fault in emphysema is not in the bony thorax There is much evidence which indicates that the chief defect in emphysema is a loss in pulmonary elasticity consequent to disease of the lungs, or to senility. Loss of elasticity affects pulmonary function in many ways The lungs do not collapse normally in expiration and become abnormally voluminous, thereby increasing the residual and functional residual air and lowering reserve and complemental air volumes Failure of the lungs to collapse normally in expiration requires that expiration be associated with active effort, instead of being purely passive as it is normally.

Increased functional residual air volume changes the ratio between the tidal air and the volume of air remaining in the lungs at the end of expiration and so impairs mixing of the tidal air with the air left in the lungs; this may be accentuated by structural changes in the lungs themselves, that is, by impaired expansibility. The decrease in complemental air is an indication of the reduced expansibility of the lungs, which in some cases is sufficient to lower the total volume even at rest Anoxia tends to occur as a consequence, as does hypercarbia also In addition, the greatly increased volume of the lungs in respiratory diastole leads to flattening of the diaphragm; the loss of the normal arched diaphragmatic contour lowers respiratory efficiency greatly. Loss of much or all of the normal negativity of intrapleural pressure also impairs respiratory efficiency.

It is clear that a variety of factors gives rise to poor mixing in the lungs; carbon dioxide retention and lowering of arterial blood oxygen saturation may occur in spite of a compensatory increase in respira-

Hurtado *et al.*, 1935); it may fall further during exercise (Himwich and Loebel, 1927), or show no consistent change (Goggio, 1944); the response apparently depends on the severity of the disease and the violence of the exercise When low, it rises when high concentrations of oxygen are breathed (Goggio, 1944). The arterial blood carbon dioxide content is often high (15; Scott, 1919, 1920); the venous blood carbon dioxide content is also increased (Scott, 1919, 1920; Essen *et al.*, 1923). The general statement has been made also that patients with pulmonary disease often have an elevated arterial carbon dioxide content (Campbell *et al.*, 1923; Fraser, 1927; Fraser *et al.*, 1928; Porges *et al.*, 1913), some of these patients probably had emphysema. The arterial blood carbon dioxide may fall with mild exertion (Goggio, 1944). Patients with emphysema may have low tissue oxygen and high tissue carbon dioxide tensions (Seevers *et al.*, 1936) and the bone marrow may be anoxic (Berk *et al.*, 1948).

Blood carbonic anhydrase. — The blood carbonic anhydrase level is reported as normal by Lambie (1938). However, more recent work, employing a more accurate method, has shown that severe emphysema with polycythemia causes a rise in carbonic anhydrase activity in the blood (Altschule and Lewis, 1947).

Blood electrolytes and pH. — The alkali reserve is high in severe emphysema (Scott, 1920; Dautrebande, 1925); it has also been reported high in severe pulmonary disease in general (Fraser, 1927). Accordingly, although carbon dioxide retention occurs, the blood pH is normal or only slightly lowered (Scott, 1920; Dautrebande, 1925; Fraser, 1927; Campbell *et al.*, 1923; Cobet, 1924). However, it falls with only mild exertion (Goggio, 1944). The increased alkali reserve of emphysema is associated with increased tolerance to breathing high concentrations of carbon dioxide (Reinhardt, 1912; Scott, 1919, 1920; Christie, 1934); that is, carbon dioxide causes less hyperpnea in patients with emphysema than in normal subjects or cardiac patients. Elevated blood bicarbonate levels are commonly associated with low blood chloride concentrations in pulmonary emphysema (Essen *et al.*, 1923); the presence of emphysema or other chronic pulmonary disease may distort or abolish the usual pattern found in congestive failure, namely, low bicarbonate and high chloride levels (page 80).

Blood. — Normal or only slightly increased values for plasma or

The polycythemia that may develop compensates in part for the effects of anoxia. In addition, however, polycythemia is accompanied by an increase in blood carbonic anhydrase activity, which also is useful when carbon dioxide excretion in the lungs is slowed The increase in blood base available for formation of bicarbonate also acts to compensate for carbon dioxide retention. It is possible that other mechanisms not yet understood may also be effective in causing tolerance to carbon dioxide (Barbour and Seevers, 1943).

The circulation at rest is not affected by lesser degrees of pulmonary emphysema As the latter increases in severity, slight elevation of venous pressure, secondary to increased intrathoracic pressure, develops. This impairment of venous return does not result in reduced cardiac output at rest, but may prevent normal increases during exertion. Increased intrapulmonary vascular pressure and accelerated circulation due to anoxia may combine to cause myocardial failure ultimately The superimposition of changes due to myocardial insufficiency upon the high venous pressure and polycythemia that may exist as a consequence of emphysema gives rise to very marked degrees of venous engorgement and cyanosis, this condition is called "right-sided failure" by clinicians, although it is apparent that its causative mechanisms are complex.

The possible role of anoxia in the causation of disturbances in gastro-intestinal motor function, and of hypercarbia in changes in gastric secretion have been pointed out (page 307)

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Chapter VIII

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tory rate and minute volume at rest. The respiratory inefficiency and the limitation of tidal air volume become more pronounced in exercise, and although the rate and minute volume are often greatly increased, oxygen intake does not increase adequately and arterial blood oxygen saturation may fall; breathing oxygen during work prevents these changes. The oxygen debt is of course abnormally high in emphysema.

A few data indicate that abnormal lactic acidosis occurs during work in patients with emphysema (Goggio, 1944), this is probably related to anoxia, for it has been shown that work done even by normal subjects under anoxic conditions elevates blood lactate levels abnormally (page 88). It is significant in this regard that lactate *tolerance may be impaired in chronic pulmonary disease* (Crisafulli and Colacresi, 1937).

Dyspnea on exertion in patients with emphysema is the consequence of lowered arterial blood oxygen, increased arterial blood carbon dioxide, lactic acidosis and the general inefficiency of breathing, which greatly increases the effort necessary to obtain a given tidal volume. The tendency toward carbon dioxide acidosis at rest, however, is minimized by the high alkali reserve. The question whether reflexes from the overdistended lungs, that is, the Hering-Breuer reflex, or from distended pulmonary arteries also contribute to dyspnea cannot be settled; these reflexes may well be of some importance. The cyanosis of emphysema is due solely to lowered arterial blood oxygen saturation and, in accord with the small changes in the latter usually found, is commonly mild.

Some relief of the respiratory symptoms of emphysema is afforded in occasional instances by the use of a procedure suggested by the observed changes in function in that disorder. The loss of elasticity of the lungs leads to flattening of the diaphragm, so that the function of the latter is greatly impaired as its excursion is limited. Elevation of the diaphragm by means of a snug but not tight abdominal binder restores the normal diaphragmatic arch, so that that organ can function in a manner more nearly normal (Alexander and Kountz, 1934; Kountz and Alexander, 1934; Meakins and Christie, 1934). Too tight a binder, however, aggravates respiratory symptoms.

The remarkably small amount of dyspnea often seen in severe emphysema has been a matter of comment by many *clinical writers.*

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IX

BRONCHIAL ASTHMA

The respiratory dynamics during asthmatic attacks are very much like those of chronic emphysema, with an additional superimposed element of bronchial obstruction.

Lung volume and its subdivisions. — The residual air is usually described as increased (Anthony, 1930; Hurtado *et al*, 1935*a*, *b*; Roelsen, 1938); only Bohr (1907) found it normal. The reserve and complemental airs (Bohr, 1907; Anthony, 1930; Knipping *et al.*, 1932) are much reduced; the vital capacity is considerably decreased in volume (1; Myers, 1922). The total capacity may be normal or low (Bohr, 1907; Anthony, 1930, Hurtado *et al*, 1935*a*).

Intrapleural pressure. — Kountz *et al.* (1932) found the static intrapleural pressure, that is, the intrapleural pressure during respiratory diastole, high in asthma, but Christie and McIntosh (1934) reported it as normal It is apparent that either condition could occur under different circumstances Changes in the dynamic intrapleural pressure do, however, occur, for von Neergard and Wirz (1927), Christie and McIntosh (1934), Paine (1940) and Kountz *et al.* (1932) found it more negative than normal in inspiration and more positive in expiration. Prinzmetal (1934), however, reported it to be more negative than normal at all times, an observation which is difficult to accept.

Respiratory dynamics. — Mixing in the lungs is impaired (Roelsen, 1938, 1939). The inspiratory velocity of air flow in the larger airways is slightly diminished, while the expiratory velocity is greatly reduced (von Neergard and Wirz, 1927, Gross, 1943); the expiratory pressure is, however, normal (Gross, 1943). Pulmonary elasticity is described as impaired (von Neergard and Wirz, 1927; Paine,

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time (Miller, 1934; Hitzig, 1935; Oppenheimer and Hitzig, 1936), and the amyl nitrite time (Gross, 1945) are normal or somewhat reduced in asthmatics. In addition, the normal or short arm-to-tongue or -face or ether times reported for patients with unspecified types of pulmonary disease (page 313) probably include data on some asthmatic persons.

Venous pressure. — Most authors report a rise in venous pressure during attacks (4; Meyer and Middleton, 1929); however, the values need not be outside the normal range (von Gönczy, 1930, Wartman, 1935; Oppenheimer and Hitzig, 1936, Kroetz, 1922). The rise that occurs is probably secondary to increases in intrathoracic pressure.

Blood carbonic anhydrase. — The blood carbonic anhydrase level is reported to be normal (Lambie, 1938).

Symptoms. — The cardiorespiratory dynamics of asthma during attacks resemble closely those of chronic pulmonary emphysema (page 310), since the bronchospasm of the attack gives rise to a type of acute emphysema The bronchospasm in itself also exaggerates the difficulties in intrapulmonary mixing and thereby favors the more rapid and severe development of anoxia and hypercarbia The symptomatology during attacks is usually dominated, however, by the sensation of strangulation and emotional reactions to it. Nevertheless, during protracted attacks, it is possible to discern effects of anoxia in the form of clouding of the mental faculties and progressive cyanosis.

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Chapter IX

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1940); however, this finding may be an artifact caused by marke bronchoconstriction, that is, the lung as a whole acts like a les elastic body than normal in attacks, but the parenchyma itself is no less elastic. The maximal possible ventilation may be markedly decreased (Knipping, 1935, Zaeper and Wolf, 1939). The tidal air at rest is smaller than normal according to most authors (von Neergard and Wirz, 1927, Houssay and Berconsky, 1932; Campbell and Poulton, 1926; Paine, 1940); only Staehelin and Schütze (1912) found it large in some cases. The rate is increased, so that the minute volume of respiration is normal or even high (2, Campbell and Poulton, 1926). The ventilation equivalent — the volume of air breathed per hundred cubic centimeters of oxygen absorbed — is within normal limits at rest (Herbst, 1928; Jansen *et al.*, 1932; Knipping *et al.*, 1932). In exercise the tidal air increases less than normal (Campbell and Poulton, 1926), however, the rate rises excessively, so that the increase in respiratory minute volume is approximately normal or above it (Herbst, 1928, Campbell and Poulton, 1926). This type of change in respiratory dynamics makes for inefficient breathing The oxygen intake during work is not adequately increased for the task (Herbst, 1928) unless air enriched with oxygen is breathed (Zaeper and Wolf, 1939); the oxygen debt after work without oxygen is consequently large and prolonged (Herbst, 1928; Nylin, 1938).

Blood gases; tissue gas tensions. — The arterial blood oxygen saturation falls in attacks (Houssay and Berconsky, 1932; Knipping, 1935; Kroetz, 1929; Meakin, 1921); it rises to or toward normal when air enriched with oxygen is breathed (Meakins, 1921). Carbon dioxide retention occurs in asthmatics, elevating the level in the arterial blood (Houssay and Berconsky, 1932; Knipping, 1935); a similar change occurs in the tissues (Seevers *et al.*, 1936; Sibree, 1941). The tissue oxygen tension is described by Seevers *et al.* (1936) as low, and by Sibree (1941) as within normal limits. As has been pointed out elsewhere (page 85), measurements of tissue tensions of carbon dioxide are more likely to be accurate than are those of oxygen.

Circulation time. — No studies of cardiac output during asthmatic attacks are available, but many studies of circulation time have been made. The arm-to-tongue or -face time (3; Cottrell and Cuddie, 1942), the carbon dioxide time (Grubner et al. ...

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The reserve air, however, increases markedly, often to more than double its original value (Altschule and Zamcheck, 1944); it is often diminished almost to zero when fluid is present, so that even though it may be doubled after a tap, it contributes little toward increasing the vital and total capacities. The functional residual air is also increased somewhat after thoracentesis (Altschule and Zamcheck, 1944).

Late effects of thoracentesis. — Further large increases in reserve and functional residual air volumes occur during the month following thoracentesis, with smaller increases in residual air. The complemental air, and consequently the vital capacity, likewise show slow though marked increases; the total capacity also becomes considerably larger (Altschule and Zamcheck, 1944).

Respiratory dynamics — The tidal air volume is often lowered by pleural effusion and since the rate is usually increased, the respiratory minute volume is normal or slightly above normal (Knipping *et al*, 1932, Altschule and Zamcheck, 1944). The maximal possible ventilation per minute is diminished (Knipping, 1932). The intrapleural pressure is high and may actually rise above atmospheric (Clark, 1915; Shattuck and Welles, 1919); it falls after thoracentesis.

Blood gases. — The arterial blood oxygen saturation is usually not lowered by pleural fluid, although in some instances decreases have been found (LeBlanc, 1922; Ihaya, 1934; Altschule and Zamcheck, 1944); thoracentesis increases low values to or toward normal. The arterial blood carbon dioxide is usually not outside the range of normal (LeBlanc, 1922, Altschule and Zamcheck, 1944); in the presence of dyspnea and hyperventilation, it may be lowered somewhat (Porges *et al*, 1913).

Cardiac output. — Studies of cardiac output and arteriovenous oxygen difference by various methods have usually yielded normal values (LeBlanc, 1922; Ringer and Altschule, 1930; Ihaya, 1934; Altschule and Zamcheck, 1944); very large effusion may lower the cardiac output somewhat (Ihaya, 1934). Busacchi (1938) reported that he found the cardiac minute volume output to be quite low in most of his patients, with return to normal after clearing of the effusion His observations, however, are not entirely applicable to the present discussion, since at least some of his patients had adhesive

X

PLEURAL EFFUSION

Pleural effusion commonly complicates many diseases and its manifestations may alter or overshadow those of the underlying disorder. The severity of the respiratory symptoms associated with pleural effusion varies markedly from patient to patient and depends not only on the volume of fluid in the pleural space, but also on the nature of the disease causing the effusion. Appreciation of the functional changes caused by pleural effusions makes these variations intelligible.

Lung volume and its subdivisions. — Early reports of measurements on the subdivisions of the lung volume, exclusive of vital capacity, are fragmentary and based on methods no longer considered reliable (Siebeck, 1910, Bittorf and Forschbach, 1910; Plesch, 1913; Peters and Barr, 1920); in addition, the fact that the lungs themselves are often the site of disease in patients with effusions makes the interpretation of absolute values difficult. Recent studies show that the functional residual, reserve and complemental airs and the vital and total capacities are considerably diminished by pleural effusion, while the residual air shows little or no decrease (Altschule and Zamcheck, 1944); other authors have also found a decreased vital capacity in patients with pleural fluid (1; Myers, 1925).

Immediate effects of thoracentesis. — The vital capacity shows little or no immediate increases after a chest tap, in spite of the fact that dyspnea may be relieved (Peabody and Wentworth, 1917; Graham, 1920;Bendove, 1925; Altschule and Zamcheck, 1944). Similarly, the complemental air shows no significant change and the total capacity is but slightly increased (Altschule and Zamcheck, 1944).

of negativity of the intrapleural pressure. Indeed, measurements of the intrapleural pressure in such patients demonstrate the loss of all or most of the normal negative pressure Following thoracentesis, the reserve air increases markedly and the intrapleural pressure becomes more negative. Decreased negativity of the intrapleural pressure, consequent to any cause, impairs the efficiency of respiration and also influences cardiovascular dynamics, in a manner that will be discussed below.

The complemental air, a measure of the expansibility of the lungs, is markedly diminished by pleural fluid. This fluid acts to decrease pulmonary expansibility in two ways· (i) by occupying space within the thorax and (ii) by causing atelectasis, the atelectatic lung being less expansible than the normal. Although the complemental air in patients with effusions does not decrease to the volume of the resting tidal air, it is in some instances sufficiently small to prevent the normal increase in tidal air during exercise. It has been shown that there is a decrease in maximal respiration during exertion in patients with pleural effusion The decrease in complemental air that occurs in patients with pleural effusion therefore makes for anoxia during exertion, and consequently contributes to dyspnea. Decreased arterial oxygen saturation is found only occasionally in patients studied at rest, but would probably occur in many more during severe exertion. Impaired expansibility of the lungs also favors dyspnea by requiring that the patient expend more effort in attaining a given tidal air volume; the tidal air volume is often decreased before removal of fluid. The complemental air is affected little by thoracentesis, attaining its normal volume only with complete reexpansion of the atelectatic lung in the weeks following removal of the fluid.

Early observers of the vital capacity noted that although it is low in patients with pleural effusion, it is only slightly increased immediately after thoracentesis. The vital capacity is the sum of the reserve and complemental airs; the latter is much larger than the former, so that its lack of change overshadows the marked changes in reserve air after pleural fluid is removed. The vital capacity returns to normal with the complemental air some weeks after chest tap. It is apparent that study of the vital capacity in patients with pleural effusion affords no accurate information on the state of pulmonary function.

mediastinopericarditis. Moreover, his data on normal subjects ar so variable as to suggest some error in procedure.

Circulation time. — The arm-to-tongue time is normal (2; Alt schule and Zamcheck, 1944); the ether time is likewise norma (Hitzig, 1935; Vecchi, 1937).

Venous pressure. — The venous pressure may be either normal or somewhat elevated in patients with pleural effusion (3; Clark, 1915). No matter what its level, following thoracentesis some decrease is the rule (Clark, 1915; Taylor *et al.*, 1930; Grellety-Bosviel, 1930; Altschule and Zamcheck, 1944; Schirosa, 1947). This fall in venous pressure has been correlated with corresponding changes in intrapleural pressure caused by removal of pleural fluid (Clark, 1915; Shattuck and Welles, 1919).

Symptoms. — The decrease in functional residual air, that is, the space available for breathing, caused by pleural effusion is ordinarily not large enough to influence respiration in itself. However, the functional residual air rises somewhat immediately after thoracentesis and therefore it is apparent that pleural effusion causes atelectasis, the collapsed lung reëxpanding to some extent with removal of the thoracic fluid. Complete reëxpansion, as measured by the functional residual air, does not, however, occur for three or four weeks. Accordingly, overcoming of the atelectasis must be regarded as only of contributory importance in the immediate relief of dyspnea that may occur with thoracentesis.

Since the removal of large amounts of fluid from the chest is followed by an immediate increase in functional residual air of only a few hundred cubic centimeters, it is clear that elevation of the diaphragm must occur during thoracentesis. The diaphragm, pushed down and flattened by pleural effusion, resumes its normal arched contour as fluid is withdrawn. In its depressed, flattened state, the diaphragm is in a position that permits only limited excursion and makes for inefficient respiration; after resumption of its normal arch, diaphragmatic respiratory excursion is greatly increased and respiration becomes more efficient. This is in harmony with the clinical observation that patients with dyspnea associated with pleural effusion show active use of the accessory muscles of respiration, which is abated by thoracentesis.

The marked decrease in reserve air indicates a corresponding loss

patients with pleural effusion are not to be considered contradictory, since they did not study their patients before and after tapping. The fall in venous pressure that occurs after thoracentesis is of particular interest because it may explain the occurrence of diuresis in some cardiac patients following this procedure

Impairment of venous return tends to cause decreased cardiac output. However, the cardiac output at rest in patients with uncomplicated pleural effusion is found to be normal except in occasional instances, when it may be slightly decreased, this is in harmony with the recorded observations on circulation time. Although some obstruction to the return of blood from the periphery exists because of decreased negativity of intrapleural pressure, it appears that enough pressure is built up in the veins that flow is not decreased and that cardiac output therefore remains unchanged in these patients at rest. It is probable, however, that the increase in cardiac output in exercise in patients with hydrothorax would be less than normal. The possibility that impaired cardiac function may result from extreme degrees of pressure on the heart or from mediastinal displacement cannot be evaluated on the basis of the data available.

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Chapter X

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It is clear from all of the foregoing discussion that pleural effusion acts in many ways to impair respiratory function. Nevertheless, many patients with large effusions exhibit little or no discomfort, at least while at rest. In this connection it is important to bear in mind that although the tidal air volume is usually decreased, the functional residual air volume is lowered also. Thus the ratio between the air taken with each breath and the air remaining in the lungs after the end of expiration is not changed greatly; mixing is therefore unimpaired. The changes in pulmonary function caused by hydrothorax are, however, similar in some ways to those consequent to emphysema, diffuse pulmonary fibrosis and chronic congestive failure. Accordingly, patients with diffuse pulmonary disease — emphysema, fibrosis or congestion — are more likely to exhibit dyspnea and orthopnea when pleural fluid develops than are other patients. The severity of these respiratory symptoms varies not only with the volume of fluid in the pleural spaces, but also with the severity of the underlying pulmonary disease. Conversely, if a patient obtains marked relief from respiratory discomfort following a relatively small thoracentesis, it is likely that he also has some diffuse pulmonary lesion.

The effects of thoracentesis may be summarized as follows:

Immediate:

(1) Increased negativity of intrapleural pressure;
 (a) Improved respiratory efficiency,
 (b) Improved venous return;
(2) Removal of bulk of fluid;
 (a) Removal of restraint on respiration,
 (b) Restoration of diaphragmatic arch,
(3) Some reëxpansion of collapsed lung,

Late:

(1) Reexpansion of atelectasis;
 (a) Increased respiratory space,
 (b) Restoration of expansibility of lung.

The above-discussed changes in intrapleural pressure in patients with pleural effusion impair venous return, for although the venous pressure is often not elevated above normal in the patients without congestive failure, it falls following throacentesis. The findings of various authors that the venous pressure is within normal limits in

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Le [illegible]
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air and the vital capacity, must be diminished and has been found so by all authors (6, Cournand *et al.*, 1941).

Respiratory dynamics. — The volume of air moved by each breath may be normal or decreased, depending on the size of the pneumothorax and the presence of pain (7; Leiner, 1944; von Neergard and Wirz, 1927). However, the rate usually increases (Richards *et al.*, 1932, Hirschsohn and Maendl, 1922), accordingly, the respiratory minute volume is normal or increased somewhat (Means and Balboni, 1916, Hirschsohn and Maendl, 1922; Knipping and Moncrieff, 1932; Richards *et al.*, 1932; Leiner, 1944). The oxygen consumption does not deviate from the normal (Bluhm, 1935; Leiner, 1944); accordingly the ventilation equivalent, that is, the volume of air breathed per hundred cubic centimeters of oxygen absorbed, is normal or elevated (Knipping and Moncrieff, 1932; Leiner, 1944). The alveolar carbon dioxide content may be lowered if hyperventilation is present (Richards *et al*, 1932). The degree to which ventilation per minute can increase in response to increased needs is considerably lowered in some patients with pneumothorax (Cournand and Richards, 1941; Leiner, 1944). The oxygen debt is described as normal or increased, and prolonged (Bluhm, 1935; Nylin, 1933, 1937), depending apparently on the size of the pneumothorax, the degree of antecedent pulmonary disease and the amount of work done in the test. Interesting measurements of the exact amount of depression of respiratory function of the collapsed lung and of the compensatory changes in function of the other have been made in patients with pneumothorax (Leiner, 1944, Pinner *et al.*, 1945).

Blood gases — Changes in arterial oxygen saturation at rest usually do not occur, although occasional slight decreases have been noted (8, Richards *et al.*, 1932). The arterial carbon dioxide content is normal as a rule (Christie, 1936, LeBlanc, 1922, Pomplun, 1928), however, if significant hyperpnea and lowering of alveolar air carbon dioxide occur, it is decreased (Richards *et al*, 1932). The blood pH remains in the normal range, however (Richards *et al*, 1932). Pulmonary function, usually quite adequate at rest, may become insufficient during exertion, so that carbon dioxide retention may occur (Cournand and Richards, 1941).

Cardiac output. — The minute volume output of the heart is slightly or moderately reduced relative to metabolic needs, so that the

XI

PNEUMOTHORAX

Lung volume and its subdivisions. — All published data are in agreement that the functional residual air volume decreases moderately when pneumothorax occurs (1; Christie, 1936). Moderate decreases in residual air, due to collapse of the lung, have also been found (2, Richards *et al*, 1932). The contrary conclusions of Wolf (1928) are based upon an inaccurate method for measuring residual air and are not acceptable. Very marked diminution in reserve air, to the point of its disappearance in some cases, has been described (3; Leiner, 1944). In a given case the volume of the reserve air varies with the negativity of the intrapleural pressure, so that decreases in the former are to be expected when the latter approaches or exceeds atmospheric pressure.

The complemental air is also diminished, since the air in the pleural space prevents the normal expansion of the lungs during forced inspiration (4; Leiner, 1944). At times the complemental air may decrease so much as to approach the tidal air volume (Anthony and Heine, 1930). Tobiesen (1911) found the complemental air to be normal in his studies.

The sum of the reserve and complemental air volumes is the vital capacity, which of course is diminished (5; Myers and Bailey, 1925, Bendove, 1925). The decrease in vital capacity that occurs in a patient with induced pneumothorax is less than the volume of air injected, often strikingly so. One reason for this phenomenon is the decrease in residual air, but there must be, in addition, some flattening of the diaphragm to account for the marked discrepancy that often exists. The total capacity, since it is the sum of the residual

mixing and diffusion Accordingly, a decrease may make for increased efficiency of respiration, possibly accounting for the surprising lack of dyspnea in some instances. On the other hand, a decrease in this volume implies a smaller area of respiratory epithelium exposed to aeration; this decrease is not significant unless the patient already has extensive disease resulting in decreased area available for respiratory exchange, or some other derangement of pulmonary function.

The marked diminution in reserve air that occurs in pneumothorax is significant only in that it parallels the change in intrapleural pressure; decreased negativity of the intrapleural pressure decreases the efficiency of respiration somewhat and in addition gives rise to the changes in cardiovascular function discussed below. Decreased complemental air volume indicates impaired expansibility of the lung; the latter may be very much diminished in pneumothorax, thus accounting for the tendency of the tidal air volume to fall at rest, with a compensatory increase in rate and, since shallow respiration is relatively inefficient, in minute volume also. This restriction of expansibility may be of great importance during exertion, for it prevents the normal considerable increase in tidal air that should occur. The maximal possible ventilation actually has been shown to be decreased, so that the finding of carbon dioxide retention and increased and prolonged oxygen debt after exercise in some patients is not unexpected The vital capacity merely reflects the changes in reserve and complemental air volumes and in itself, therefore, has no precise significance.

It is apparent that the changes in the subdivisions of the lung volume, while they usually cause no great impairment of pulmonary function at rest, may give rise to respiratory insufficiency during exercise. That anoxic changes which occur are not greater is consequent to the fact that, while the oxygen-absorbing function of the collapsed lung is greatly diminished and the ventilatory function somewhat decreased, compensatory increases in these functions on the other side occur, as shown by bronchospirographic studies (Leiner, 1944; Pinner *et al.*, 1945).

A pneumothorax that is large enough in a given case to raise the intrapleural pressure significantly will result in some rise in venous pressure, in some cases the latter need not necessarily rise above the

arteriovenous oxygen difference is often somewhat increased (Richards *et al.*, 1932; Bluhm, 1935; Cournand *et al.*, 1935; Stewart and Bailey, 1940); in general, however, the changes are small, and Nylin (1933) found no change in his patients.

Circulation time. — The arm-to-tongue time is normal or slightly reduced (9; Hurst and Brand, 1937). Reduction may be due to *shortening of the average pathway through the lungs as a consequence of collapse* of some of the parenchyma. The arm-to-lung (ether) time is normal or slightly reduced (Hitzig, 1935; Feinsilver, 1943).

Venous pressure. — Depending apparently on the degree of change in intrapleural pressure, the venous pressure has been found to be within normal limits or somewhat elevated (10; Hussey, 1936).

Right heart pressures. — The right auricular and right ventricular pressures are not influenced significantly by pneumothorax in man (Bloomfield *et al.*, 1946).

Arterial pressure. — No striking changes in arterial blood pressure occur except in some patients with massive spontaneous pneumothorax; here the systolic and pulse pressures may fall markedly, with lesser declines in diastolic, and the patient may exhibit signs of collapse.

Symptoms. — Patients who receive pneumothorax therapeutically ordinarily show little or no respiratory embarrassment following the intrapleural administration of air; although a considerable degree of pulmonary collapse may be induced in some instances, intrapleural pressures are not permitted to become excessively high and, moreover, the patients are not likely to engage in strenuous exertion thereafter. In some instances, however, and in many with spontaneous pneumothorax, severe respiratory or circulatory symptoms occur. The size of the pneumothorax and the level to which the intrapleural pressure rises evidently largely determine the occurrence of untoward manifestations. Equally important, however, is the presence or absence of extensive pulmonary disease in the uncollapsed lung. These considerations probably account for the variations in the observations reported.

The decreases in residual, and more particularly in functional residual air, that is, the amount of air in the lungs after normal expiration, diminish the volume of air that must be exchanged by

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upper limit of normal. The loss of the normal negative intrapleural pressure impedes venous return; although the cardiac output may fall, it need not diminish significantly, since enough pressure may be built up in the peripheral veins to force this slight barrier. However, it is to be doubted that the cardiac output under such circumstances can increase in a normal fashion in response to exercise. This fact in itself may lead to an abnormally large oxygen debt after work. Although marked changes in circulation do not occur at rest, mild circulatory insufficiency may occur during exercise.

Collapse of the lung such as occurs in pneumothorax so shortens the average length of the pathway traversed by the substance used in measuring the circulation time as to reduce the latter somewhat. This acceleration of the circulation may be masked by a tendency toward slowing parallel with a reduction in cardiac output. In the case of a large spontaneous pneumothorax, circulatory function may be so markedly impaired by the change in intrapleural pressure as to give rise to a sudden fall in cardiac output severe enough to produce the picture of shock This is particularly likely to occur if positive pressures develop in the pleural space; release of these high pressures or withdrawal of the air usually gives rise to rapid improvement.

The common development of effusions in a pneumothorax is explained by the results of experiments in dogs performed by Dolley and Wiese (1929). These authors found that pneumothorax reduces lymph flow and retards the taking up of material from the pleural space.

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Chapter XI

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XII

PNEUMONIA

The cardiorespiratory manifestations of pneumonia are largely determined by the changes due to fever, the latter have been reviewed elsewhere (Altschule and Freedberg, 1945). The function of the circulation and respiration in pneumonia may be further modified by the occurrence of certain complications such as marked anoxia, abdominal distention, pleural effusion or pericarditis, most of which have already been discussed. Accordingly, the present discussion will involve consideration of the immediate changes caused by the modifications of pulmonary structure consequent to a pneumonic process; these are of minor importance unless a good deal of the parenchyma of the lung is affected.

Lung volume and its subdivisions.—The accuracy of measurement of the subdivisions of the lung volume is often impaired to a large extent by the occurrence of pleuritic pain, which may result in false low readings for reserve air, complemental air, and vital capacity; in addition, by causing extremely shallow breathing, pleuritic pain may sometimes cause inaccurate results when the residual air is measured. The functional residual air is reported decreased by all authors (Siebeck, 1910; Binger and Brow, 1924; Lindskog *et al.*, 1936, Kaltreider *et al*, 1937); a certain degree of parallelism between the amount of this reduction and the extent of the pneumonic lesion appears to exist. The residual air is normal or somewhat reduced in volume (Siebeck, 1910; Lindskog *et al.*, 1936, Kaltreider *et al.*, 1937). The reserve air, vital capacity and total capacity usually show marked decreases (Siebeck, 1910, Myers, 1922; Lindskog *et al.*, 1936; Kaltreider *et al.*, 1937). Following subsidence of the

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1935). Here again it is impossible to evaluate the role of fever and other influences in addition to changes in the lungs themselves.

Venous pressure. — Normal values for venous pressure have been found by most observers (3; Kastlin and MacLachlan, 1931); Moore (1937), however, described it as elevated A late rise in venous pressure may occur in patients who are doing poorly (Fuchs, 1921; Kastlin and MacLachlan, 1931). The rise in venous pressure during exertion is normal in patients with pneumonia (Schott, 1912).

Symptoms. — Symptoms due solely to the pneumonic lesion in the lungs may be greatly overshadowed by those of fever, anoxia, pericarditis, pleural fluid, and so on.

The above-described decrease in functional residual air diminishes to a variable extent the space available for breathing; this is hardly of significance, except in patients in whom most of the lung tissue is involved. The elasticity of the lung is somewhat impaired, as is shown by the decreased reserve air. The latter finding, although it is evidence of some lessening of the negativity of the intrapleural pressure, indicates no great change in that direction Decreased expansibility of the lung, shown by the considerable decrease in complemental air and in maximal possible minute ventilation, is probably consequent both to pleuritic pain and to increased rigidity of the lungs caused by congestion, interstitial edema and exudate.

Except in extreme cases, the decreased pulmonary expansibility is not likely to be of primary importance in the genesis of dyspnea or hyperventilation in patients with pneumonia, in spite of the increased oxygen consumption caused by fever The shallow tidal air volume that occurs is largely due to pleuritic pain, increased pulmonary rigidity playing only a minor role. A considerable increase in respiratory rate and minute volume may partly or wholly compensate for shallow respiratory exchange. This increased respiratory activity, however, is only partly consequent to anoxia, for it is often not markedly influenced by oxygen; two additional causative factors are fever and, as first shown by Porter and Newburgh (1916, 1917), reflex stimulation of the respiratory center by irritation of pulmonary parenchyma.

The lowered arterial blood oxygen saturation that is common in patients with extensive pneumonia appears to be largely consequent to impaired diffusion of oxygen in the damaged lungs and to the flow

fever, the changes in the subdivisions of the lung volume may persist for two months or more (Kaltreider *et al.*, 1937).

Respiratory dynamics. — The respiratory minute volume is increased in pneumonia (Beddard and Pembrey, 1908; Meakins, 1920; Binger and Davis, 1928; Knipping and Moncrieff, 1932); this occurs as a consequence of a marked rise in respiratory rate (Meakins, 1920; Binger and Davis, 1928). The tidal air volume falls as a rule, often markedly (Meakins, 1920; Binger and Davis, 1928; Lindskog *et al.*, 1936). The increased respiratory activity may result in a fall in alveolar carbon dioxide content (Beddard and Pembrey, 1908); the amount of air breathed per hundred cubic centimeters of oxygen absorbed rises (Knipping and Moncrieff, 1932), so that respiration becomes less efficient The maximal possible respiration per minute is considerably diminished (Jansen *et al.*, 1932). It should be noted that much of this change, or in some cases all, might be due to fever alone (Altschule and Freedberg, 1945).

Blood gases; tissue gas tensions — A decrease in arterial oxygen saturation has long been recognized to be of common occurrence in pneumonia (1; Barach and Woodwell, 1921; Stadie, 1919); the beneficial effects of the administration of oxygen have been established (Barach and Woodwell, 1921; Binger, 1928; Meakins, 1921; Stadie, 1922). Changes in arterial carbon dioxide concentration are more variable, high, normal, or low values being reported (2; Barach and Woodwell, 1921, Binger *et al.*, 1927, 1928). These differences are due to the opposite effects of carbon dioxide retention on one hand, and, on the other hand, of the consequences of blowing off of carbon dioxide owing to stimulation of the respiratory center by fever, anoxia, or reflexes from the lungs (Porter and Newburgh, 1916, 1917). The arterial pH may be normal or slightly elevated (Binger *et al.*, 1927). A single report records normal or low oxygen tensions in the tissues in patients with pneumonia (Del Baere, 1939).

Cardiac output. — Lauter (1930) recorded a large increase in cardiac output, greatly in excess of the rise in oxygen consumption, in one patient, a change probably consequent to fever, although anoxia may also have played a part.

Circulation time. — The arm-to-tongue or -face time is normal or reduced (Koch, 1922; Tarr *et al.*, 1932; Hitzig, 1935; Bernstein and Simkins, 1939); the ether time is reported as normal (Hitzig,

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of blood through unaerated pulmonary tissue. Markedly shallow respiration may further lower arterial oxygen saturation (page 71). Carbon dioxide is more freely diffusible than oxygen and consequently carbon dioxide retention is of less common occurrence. Indeed, the hyperventilation consequent to fever and to reflexes arising in the lungs may far overshadow the tendency toward carbon dioxide retention, so that normal or even low values for arterial blood carbon dioxide content are common. Consequently, the arterial blood pH is usually normal or slightly alkalotic; dyspnea due to carbon dioxide acidosis is not usual.

Cardiovascular dynamics are not demonstrably influenced by the presence of a pneumonic process *per se;* whatever changes have been observed in the fragmentary studies available appear to be those of any febrile illness and, in extreme cases, of anoxia. Additional data would be helpful, however. The increased cardiac output that occurs in febrile illnesses is not sufficiently large to affect deleteriously the normal heart, but it may cause a previously damaged myocardium to fail. The occurrence of venous engorgement in elderly or cardiac patients with pneumonia who are doing poorly is difficult to interpret, since it may be the result of marked changes in intrapleural pressure consequent to massive pulmonary involvement combined with extreme degrees of abdominal distention, to congestive failure, to the development of pleural fluid, to pericarditis, or to a combination of these various factors. Whatever its mechanism, it should not be considered an indication for venesection.

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Chapter XII

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